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An integrated investigation of dementia risk factors: insights from geography, record linkage, and individual participant meta-analysis

Thomas Charles Russ

PhD by Research Publications

University of Edinburgh

2013

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Declaration

I declare that I have composed this thesis, that I have made a substantial contribution – clearly indicated – to each of the published papers, and that this work has not been submitted for any other degree or professional qualification.

Edinburgh

October 2013

Abstract

Dementia is a public health priority and its importance is projected to increase in coming decades, particularly in low- to middle-income countries. A description of the methodological challenges of observational studies and the limitations of previous attempts to combine the published literature leads me to discuss ascertainment of dementia cases and the suitability of dementia mortality as an outcome. I report the findings of a memory clinic study where 71.5% of 502 deceased individuals with probable Alzheimer dementia had dementia correctly recorded on their death certificate, which is an improvement on similar results from two decades earlier.

I review the evidence for geographical variation in dementia and discuss the implication that such variation might point towards potentially modifiable risk or protective factors for dementia. I have attempted to overcome the methodological challenges alluded to above by only examining within-study comparisons. A meta-analysis of rural-urban comparisons reveals some evidence of increased prevalence (odds ratio; 90% confidence interval (CI): 1.11; 0.79, 1.57) and incidence (1.20; 0.84, 1.71) of dementia in rural areas. These associations were stronger for Alzheimer dementia and particularly so in studies which identified early life rural residence (prevalence 2.22; 1.19, 4.16; incidence 1.64; 1.08, 2.50).

Since there are no effective treatments, there is an obvious need to focus on prevention and an urgent need to improve our understanding of the aetiology of dementia in order to attempt to prevent or delay its onset. However, it is clear that prevention must begin sufficiently early in life to have an effect – intervening in later life might be too late. I describe a body of work using the Health Survey for England cohort studies examining the association between a series of risk factors and later dementia-related death, including cardiovascular disease risk factors, psychological distress, and socioeconomic status. For example, there is a dose-response relationship between increasing psychological distress and dementia death (12-item General Health Questionnaire score 1-3 vs 0 age- and sex-adjusted hazard ratio; 95% CI: 1.44; 1.17, 1.78; score 4-12 vs 0: 1.74; 1.36, 2.22). I conclude by summarising the contribution these publications have made to the field of dementia epidemiology and by outlining ongoing and future projects building on the work presented in this thesis.

Acknowledgements

I have learned a lot over the last four years, not least that it is people that ultimately help or hinder a piece of work and, thankfully, I have met and been helped by numerous people over that time. I have been supervised during this fellowship by John Starr and David Batty. My first meeting with John was instructive – I came away with two book recommendations, one on cognitive ageing and one on New Testament Greek. He was either sufficiently foresightful or careless to take me on as a clinical research fellow based on that single meeting but working with him has been hugely stimulating and he has been an inspiring example. It is largely due to David that it has been possible for me to publish sufficient articles to seek to obtain a PhD by research publications. His energy, encouragement, and abilities have made being supervised by him very enjoyable. I am extremely grateful to them both and look forward to future years of collaboration.

Alasdair MacLullich welcomed me into the Department of Geriatric Medicine and I have been made to feel very much at home. His dynamism and enthusiasm for his subject has made it a very exciting – and enjoyable – experience getting to know him. Particular thanks should go to Lucy Eggins, Maureen Harding, and Sharon Moncrieff for their immense help. I met Ian Deary when intercalating in psychology at medical school and the enduring fascination with his research played an important role in my seeking out an academic appointment in this area. This work, in collaboration with others, has led to the founding the Centre for Cognitive Ageing and Cognitive Epidemiology, and my involvement with this centre has always been enjoyable, often stretching, but never anything less than useful. It has also been a great pleasure being part of the Scottish Dementia Clinical Research Network and I would like to thank Phil Brown, Peter Connelly, Frances Draper, and Emma Law, in particular.

My clinical research fellowship was funded by Alzheimer Scotland and, to some extent, formed the sum total of their research expenditure for a while. I am very grateful to Henry Simmons and the whole organisation for their keenness to fund research and their welcome to me. The charity must have been convinced of the value of funding research, as they went on to fund the Alzheimer Scotland Dementia Research Centre in

2011, with John Starr as director. The small but growing centre has provided a very happy home for the last two years and sharing an office with Lewis Killin and Coleen Sloan has been a great pleasure, though it has perhaps resulted in the consumption of a few too many biscuits.

I am very grateful to my NHS colleagues who have encouraged me in this relatively unusual path for an old age psychiatrist. Neill Anderson, my trainer immediately before this fellowship, provides an excellent example of a first-rate NHS clinician and has guided me carefully as a clinical supervisor during these four years. Kirstie Woodburn, the Training Programme Director for Old Age Psychiatry, has been unfailingly kind, encouraging and supportive. Bill Reid, the Postgraduate Dean, has been similarly supportive and I am very grateful to him for granting me an exceptional fourth year out of the training programme. I would also like to thank my examiners, Susie Shenkin and Craig Ritchie, for their fair and searching examination of this thesis and their helpful suggestions which have definitely improved it.

A number of the papers included in this thesis have involved a similar group of researchers from University College, London: David Batty, Mark Hamer, Mika Kivimäki, and Manos Stamatakis. They have been great fun to work with, though – apart from David – I have only met Mark in the flesh, so skilled is UCL's Department of Epidemiology and Public Health at remote working that it is possible to live in Finland or Hungary while working at UCL!

My parents, Jenny and Charles, have been unceasingly supportive throughout my life. They have encouraged me to pursue my own interests ever since announcing at the age of three that I was going to be a doctor or a frog. I am extremely thankful to them. And finally, of course, I must thank Sarah, without whom, I don't think that any of this would have been possible.

List of Figures

Publications submitted as part of this thesis

1. Russ TC, Batty GD & Starr JM (2012)
   Cognitive and behavioural predictors of survival in Alzheimer disease: results from a sample of treated patients in a tertiary-referral memory clinic. *International Journal of Geriatric Psychiatry* **27**: 844-53. (thesis pp. 48-57).

2. Russ TC, Batty GD, Hearnshaw GF, Fenton C & Starr JM (2012)
   Geographical variation in dementia: systematic review with meta-analysis. *International Journal of Epidemiology* **41**: 1012-32. (thesis pp. 58-82).

3. Russ TC, Hamer M, Stamatakis E, Starr JM, Batty GD & Kivimäki M (2013)
   Does the Framingham cardiovascular disease risk score also have predictive utility for dementia death? An individual participant meta-analysis of 11,887 men and women. *Atherosclerosis* **228**: 256-8. (thesis pp. 83-5).

4. Russ TC, Hamer M, Stamatakis E, Starr JM & Batty GD (2011)
   Psychological Distress as a Risk Factor for Dementia Death. *Archives of Internal Medicine* **171**: 1858-9. (thesis pp. 86-7).

5. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M & Batty GD (2012)
   Association between psychological distress and mortality: an individual participant pooled analysis of the Health Survey for England prospective cohort studies. *British Medical Journal* **345**: e4933. (thesis pp. 88-105).

6. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M & Batty GD (2013)
   Socioeconomic Status as a Risk Factor for Dementia Death: An Individual Participant Meta-analysis of 86 508 Men and Women from the United Kingdom. *British Journal of Psychiatry* **203**: 10-17. (thesis pp. 106-16).

Additional publications (2010-14) are shown in Appendix B (pp. 117-8)

1. Introduction

Dementia describes a cluster of neurodegenerative and cerebrovascular conditions amongst which Alzheimer disease is the most common, causing 60-80% of cases of dementia.[1] It is characterised by progressive cognitive decline – often in a number of cognitive domains but commonly involving memory – and impairment in day-to-day functioning, resulting in substantial difficulties in activities of daily living.[2] Interest has been growing in the field of dementia in recent years and increasing numbers of researchers are devoting their attention to this syndrome. It is estimated that approximately 820,000 people in the UK live with dementia, the vast majority over the age of 65 years (approximately 8% people in the UK with dementia are younger than 65 years).[3] This compares to approximately 2.3 million people in the UK with coronary heart disease.[4] Worldwide the estimated number of people living with dementia in 2010 was 36 million.[5] To give an idea of scale, if the number of people worldwide with dementia were a single country, it would have a seat at the G20.[*] This condition has a large economic cost, including health care costs and also the care needs of these, often very vulnerable, individuals. Dementia costs the UK economy £23 billion, more than cardiovascular disease and cancer combined.[3] However it is a condition which affects the person in a fundamental way and often places an enormous burden on friends and relatives who must also live with dementia.

The first topic to be discussed will be the public health importance of dementia, considering the increasing numbers of people with the condition as a result of demographic changes, as well as previous attempts to synthesise the heterogeneous epidemiological literature on dementia.

Following on from this, I will consider the methodologies used in observational dementia studies and discuss previous attempts to combine the literature. At the core of such syntheses is the method of dementia ascertainment and whether or not the methods used in separate studies are comparable. The different case-finding methodologies used in various studies will be reviewed, culminating in a discussion of record linkage and the ascertainment of dementia from mortality data, with the example

[*] The smallest G20 country in terms of population is Australia with approximately 22 million inhabitants.

of the first article in this thesis, "Cognitive and behavioural predictors of survival in Alzheimer disease: results from a sample of treated patients in a tertiary-referral memory clinic."[6] I will then go on to consider geographical variation in dementia in more detail to provide context for the second article, "Geographical variation in dementia: systematic review with meta-analysis."[7] The methodology used in this paper will be enlarged and discussed in more detail than was possible in the published version before considering the implications of non-random geographical variation in a disease. I will then discuss the findings of a recently completed study building on the work of this systematic review and meta-analysis modelling geographical variation in dementia in complementary models using the Swedish Twin Registry and the 1932 Scottish Mental Survey Cohort.[8]

Next, I will introduce life course epidemiology which suggests that factors at all stages of life could affect an individual's disease risk. I will suggest that, in view of the failure of potentially disease-modifying treatments, greater attention should be paid to preventive strategies with a view to delaying or preventing the onset of dementia. But I will also argue that intervention to modify these risk or protective factors must occur at the correct time. Thus, treating risk factors for dementia in later life might be too late. The third article in this thesis, "Does the Framingham cardiovascular disease risk score also have predictive utility for dementia death? An individual participant meta-analysis of 11,887 men and women," has similar findings showing that a risk score based on multiple cardiovascular risk factors is no better at predicting dementia than knowing a person's age.[9]

If examining traditional risk or protective factors seems to have ended in disappointment, the search for more unusual candidates has led us to psychological distress which is shown to be a risk factor for dementia death in the fourth article in this thesis, "Psychological distress as a risk factor for dementia death,"[10] and for mortality from all causes and cardiovascular disease (which shares some aetiology with dementia) in the fifth article, "Association between psychological distress and mortality: an individual participant pooled analysis of the Health Survey for England prospective cohort studies."[11] The contrasting methodology of simple pooling in the former and individual participant meta-analysis (IPMA) in the latter will be discussed.

Returning to the life course paradigm, the final article in this thesis, "Socioeconomic status as a risk factor for dementia death: an individual participant meta-analysis of 86 508 men and women from the United Kingdom,"[12] will be discussed with measures of socioeconomic status at two stages of life, before briefly discussing ongoing and planned future work building on the articles presented in this thesis. I conclude by summarising the various integrated methodologies I have used in these articles to further research into risk factors for dementia.

2. The Public Health Importance of Dementia

The rising profile of dementia, mentioned in the introduction, partly relates to demographic changes – increasing fertility rates and declining death rates. Thus, in many countries there have never been as many older people as there are now. Since there are more older adults than ever before, clearly there are going to be more people with dementia, in spite of some suggestions that the incidence of dementia may be declining as a result of improvements in cardiovascular disease risk profiles, amongst other factors.[13-15] Indeed, projected rates of dementia predict greater rises in resource-poor countries than in the rest of the world, largely due to similar demographic changes.[16] Increases in life expectancy and the benefits of health promotion, combined with the post-war 'baby boom,' whose members are now in their seventh decade, have led to substantial changes in the age structure in the UK and elsewhere. Referred to as the 'greying population' or 'squaring' of the population pyramid (Figure 1, p. 4), these changes have widespread ramifications for pension providers, health and social care services, as well as dementia epidemiologists.

However the conclusions that can be drawn from the published literature at a global scale are limited by the poor coverage of some areas of the world. There has been very little attention paid to low- to middle-income countries by epidemiological studies of dementia (Figure 2a, p. 5) and this disparity becomes even more marked when the population resident in each country, rather than the land area, is considered (Figure 2b). Thus a small minority of research attention is applied to the majority of the world's population. This may partly relate to governments prioritising basic needs – food, shelter, care – above dementia research, but even institutions in high-income countries

pay little research attention to the rest of the world, with some exceptions, such as the Ibadan-Indianapolis study.[17-20]

Figure 1. Age structure of United Kingdom, 1980-2040, with total UK population and proportion aged 65 years or over also shown. The post-war 'baby boom' can be seen as a spike around the age of 30 years in 1980, 50 years in 2000, and 70 years in 2020. Individuals aged 85 years and over were not included in these ONS data. Source: Office for National Statistics (http://www.neighbourhood.statistics.gov.uk/ HTMLDocs/dvc1/UKPyramid.html)

This neglect of a large proportion of the globe has become such a noticeable problem that a dedicated research group – the 10/66 Dementia Research Group – has been set up to remedy the situation.[21-24] The group's name refers to the 10% of research attention paid to the 66% of the population of the world with the lowest income. They have focussed their research attention on areas previously unstudied and have made important contributions to the literature.

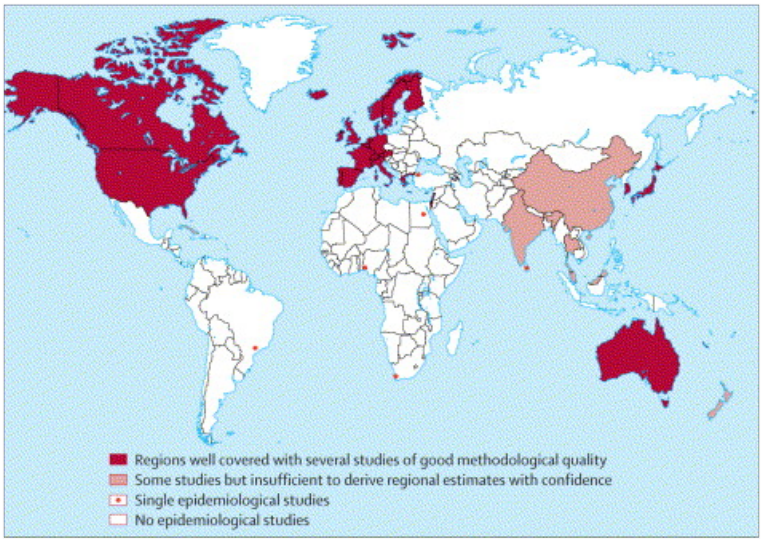
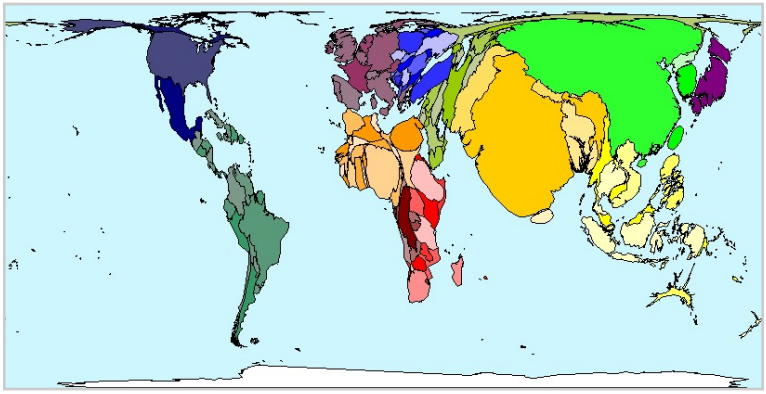


Figure 2a. Dementia prevalence studies worldwide
Source (figure and rubric - adapted): Ferri et al. (2005)[16]



2b. World population cartogram (2002). The size of each territory shows the relative proportion of the world's population living there Source (figure and rubric - adapted): http://www.worldmapper.org; Original data: United Nations Development Programme Human Development Report 2004[25]

3. Ascertainment of Dementia Cases

There have been a number of attempts to combine data from different studies and locations over the last few decades. These have ranged from narrative reviews[26, 27] to attempts to synthesise these data quantitatively.[28] Perhaps the most well-known of these are the European Community Concerted Action Epidemiology of Dementia (EURODEM)[29-31] and the more recent European Collaboration on Dementia (EuroCoDe).[32] In fact, the latter is used by the Scottish Government to estimate the number of people with dementia in the community, in order to estimate the proportion of people who receive a diagnosis, as described below. Despite their widespread use, the

interpretation of such syntheses are subject to a number of methodological difficulties which have not always been given the attention they deserve.

The first question when considering combining the results of two studies conducted independently is whether the methodologies are sufficiently similar to allow them to be compared. For example, one study which found that the prevalence of dementia was *x* in a rural area and compared this to a study done by another research group with a prevalence of *y* in an urban area might not, in fact, tell us anything about the relative rates of dementia in those two areas; we might be comparing apples with oranges. There are a number of reasons why the methodology of the two studies might not be comparable which will be considered in turn: the age structures of the populations might be different; whether the whole population was studied or a sample; one study might have used a more thorough method of case-finding than the other; the diagnostic processes followed might not be comparable; and cross-sectional versus longitudinal designs.

If the population structures of the two areas being compared or combined were vastly different, this would confound the results by age and, in itself, could explain differing rates of dementia between the areas. An extreme example would be an area exclusively occupied by young families being compared with another area with a large elderly population and a number of care homes. Thus the rate of dementia would be substantially higher in the latter area but this may be entirely explained by the different age structures of the populations.

The study of an entire population, whether a town, an island, or a whole country, is also likely to yield different results from the study of a random sample, even if the sample is of a large enough size from which to make robust inferences. Thus it is advisable that a study of a sample is not compared with the study of a population. There might be circumstances under which it would be reasonable, for example matching a comparator sample when the whole population of a particular town or island is being studied.

Thoroughness of case-finding is also likely to have an important effect of the findings of epidemiological studies in dementia. Missing data are a ubiquitous problem in observational research and missing data resulting from non-participation in a study of dementia are particularly likely to be missing in a non-random pattern, i.e. if an individual's participation or otherwise in a study relates to their dementia status.[33] This non-random missing data will consequently bias the results of the study.

The diagnostic process will also affect the findings of a study. Whether the case definitions used are comparable is the first difficulty – different diagnostic criteria, such as the World Health Organization's International Classification of Diseases (ICD) or the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), will identify different numbers of cases because they set the bar for having or not having a condition at different levels. The 10/66 Dementia Research Group is one of the few to have compared different diagnostic criteria in the same study – the narrower DSM-IV criteria and their own, broader, consensus criteria.[34, 35] They found that their results were substantially altered by using either DSM-IV or their own criteria. These data were displayed graphically in article 2, reproduced as Figure 3 (p. 8).[7] Some diagnostic criteria, for example DSM-IV, are not fully operationalized.[35] Thus, in some cases, even if the same diagnostic criteria were used in two studies, they might be differently operationalized, thus reducing their perceived comparability.

A proportion of the individuals diagnosed by the 10/66 consensus criteria, but not by DSM-IV, is likely to be at the milder end of severity. While the controversial category of 'mild cognitive impairment' (MCI) will hopefully become better defined in the future when reliable biomarkers for dementia are identified, as discussed below, the decision whether or not to include these individuals in an observational study of dementia prevalence or incidence is extremely important. Their prognosis is variable with between 10 and 20% converting to dementia each year[36, 37] but, importantly, up to 44% returning to normal each year.[38] The concept of MCI remains unclear and this lack of clarity could be ascribed to the lack of agreement on the criteria required for the value judgement inherent in its diagnosis – what should one be able to do as one gets older? Value judgements are ubiquitous in medical diagnoses yet the extent to which entities are agreed as 'illnesses' seems to be proportional to the extent to which the

criteria for the value judgements involved are settled.[39] For example, pain is almost universally agreed to be unwelcome and painful conditions are similarly seen to be illnesses without controversy. Anxiety is a more equivocal symptom since some people seek it out, for example in extreme sports, and so anxiety disorders are less clearly seen as illnesses than painful conditions. Expectations of what an eighty-year-old person should be able to do in terms of day-to-day functioning will probably vary even more and thus the status of MCI as an illness – which in the majority of definitions has function as the crucial component, the cognitive element being merely a matter of degree of impairment – is still less clear.

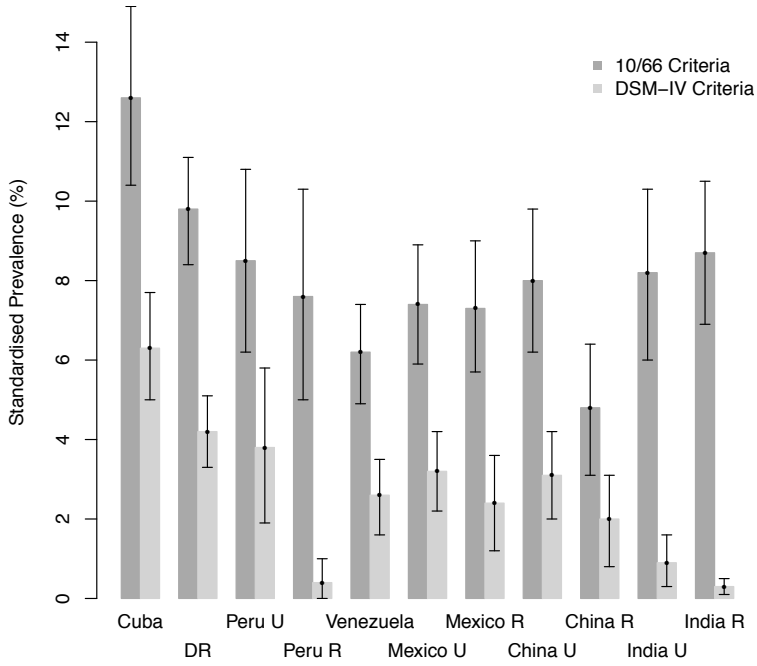


Figure 3. Comparison of standardised dementia prevalence (with accompanying 95% confidence intervals) using different diagnostic criteria. DR = Dominican Republic, U = Urban, R = Rural
Source: Constructed from 10/66 Dementia Research Group data[34] & presented in Russ et al. (2012)[7]

Diagnostic practice with regard to how to label equivocal cases of possible dementia varies widely. Indeed, some argue for a longitudinal assessment, rather than a single appointment, in order to determine with more certainty whether such an individual is likely to progress to dementia, remain the same, or return to normal cognition.[40] Due to the uncertainty surrounding a clinical diagnosis of dementia, which is nearly always no more than probable in life, it has been described as a mystery.[41] The

precursor of a mystery (i.e. MCI) could be suggested to be even more mysterious. However, it is not a mystery that we can simply ignore. The decision of whether or not to include individuals with MCI is an important one in this context – two of the studies identified in article 2 found that the variation between sites differed depending either on whether or not 'mild' cases of dementia were included (likely to overlap with the concept of MCI) or if a different cognitive test cut-off was used;[42, 43] geographical variation reduced with narrower diagnostic criteria. Once again, if two independent studies differed in their practice, MCI is another factor which makes them not comparable.

Finally, whether a study uses a cross-sectional or a longitudinal design will also affect the completeness of case-identification. This is probably more of theoretical interest as it is unlikely that a prevalence study would be directly compared with an incidence study. However, if they were, the problem of survival is introduced, which is known to vary between regions, notably across the UK.[44-46] Prevalence is related to incidence and survival and so if survival is different between two regions, prevalence and incidence – while not directly comparable in any case – are less related than they would otherwise be. Furthermore, longitudinal studies often suffer from attrition which introduces its own biases to which cross-sectional studies are not subject.

I will now outline a variety of potentially useful methodologies for observational studies of dementia. Clearly, the chosen method for identifying individuals with dementia is crucial to the quality of the study and its findings. Perhaps the most robust – only really a practical option in a relatively small area – is studying the entire population. Researchers would actively seek out all older adults living in an area (or even all adults of any age) and assess whether or not they have dementia. This methodology is resource-intensive and thus is used relatively rarely. Thus, a slightly modified version is used for robust, large-scale studies – two-phase screening. All individuals deemed to be at risk will be approached and screened, either face-to-face or by a telephone call. Those whose responses are suggestive of a possible dementia are then invited to undergo a full clinical assessment. However, in order not to miss people who might have dementia but who, perhaps because of superior premorbid abilities, were not picked up by the screening process, a random sample of those who screened negative should also be invited for

clinical assessment in order to estimate the specificity of the screening procedure. The majority of the studies included in article 2 ("Geographical variation in dementia: systematic review with meta-analysis"[7]) are a variation on this theme and this methodology has been shown to give accurate diagnoses for prevalence studies.[47] However, two-phase screening studies are not without their own biases and are subject to their own challenges and limitations, including non-participation in screening resulting in selection bias, difficulties if the screening process is not sufficiently sensitive, and the importance that validation of the screening procedure – such as clinical assessment of a sample who screened negative – is sufficiently rigorous.[33]

An interesting and powerful alternative to face-to-face follow up of research participants is using record linkage to follow their progress after recruitment. The way that medical records were viewed changed in the second half of the last century from an event-based paradigm to the idea that an individual's medical records formed a 'personal record.'[48] More recently this approach has become more sophisticated and is now a widely used approach in research.[49] The basic idea is that all contacts that a person has with the health service (and theoretically with any agency) can be collated together under their unique identifier to provide a timeline of their contacts, appointments, procedures, hospital admissions, and, ultimately, death. If each individual is uniquely identified, for example by the Community Health Index number in Scotland, deterministic linkage methods can be used, which are the most robust. Alternatively, if an individual is identified by a combination of details including name, date of birth, and sex, probabilistic linkage methods are used and an algorithm provides a linkage score and all records above a certain threshold will be allocated to that person. Since a large proportion of this methodology can be automated, it is applicable to large projects to provide 'passive follow up,' overcoming potential drawbacks of small studies, including limited power, and large studies can be conducted at relatively little cost.

Furthermore, using record linkage allows follow up to be added to cross-sectional studies in order to convert them into longitudinal cohort studies. This is the approach taken below with the annual, cross-sectional Health Surveys for England in articles 3-6.[9-12] These were designed as cross-sectional snapshots of the nation's health at a series of points in time. However, since patient identifiable data were collected and retained,

consenting participants could be subsequently traced and the causes of death recorded on the death certificates of deceased individuals examined, allowing cause-specific mortality to be investigated.

However, it is also possible to apply this methodology to surveys or groups for which research was not the primary reason for the collection of the data. This was the case with the Lothian Memory Treatment Centre (LMTC) cohort study (article 1).[6] The data were initially collected for the purposes of clinical audit in order to evaluate the service. After the initial collection of the data they were also used for research purposes in a number of cross-sectional analyses.[50-53] However, since approximately a decade had passed since the data were collected, it was possible to follow up the clinic attenders passively and identify who had died and when. Since all the patients were or had been under the care of one clinician (JMS) the approval process for the linkage was greatly simplified and merely required the approval of the NHS Lothian Caldicott Guardian. The record linkage was conducted by the Information Services Division of NHS National Services Scotland (ISD), converting this cross-sectional sample into a longitudinal cohort study.

Using dementia mortality as an outcome in an observational study begs the question whether dementia is correctly recorded on the death certificate of every deceased person who was diagnosed with dementia. This is certainly not the case. In fact, in the past, dementia recording on death certificates was not felt to be adequate for epidemiological purposes, at least in terms of investigating geographical patterns and time trends.[54] In the two decades since the publication of Martyn & Pippard's paper this situation does seem to have been improving, as article 2 demonstrates.[6] The main focus of the article was on predicting survival after diagnosis in a group of people diagnosed with Alzheimer dementia and receiving treatment in the form of a cholinesterase inhibitor. However, since it was known how many of these individuals who had subsequently died, we could examine how many of them had dementia correctly recorded on their death certificate. It is likely that the clinical diagnoses will have been robust since they had had an extensive assessment at a tertiary-referral memory clinic. The fact that 71.5% of the 502 people who died had dementia correctly recorded in any position on their death certificate is encouraging – an improvement from the 57%

reported in 1988.[54] The validity of using dementia mortality as an outcome in observational studies will be discussed further below.

However, we are left with the intriguing question of what might determine whether someone has their diagnosis correctly recorded on their death certificate. In terms of the covariates available in the dataset, we were able to demonstrate that there were no differences between those who had dementia correctly recorded on their death certificate and those who did not in terms of their premorbid IQ (p=0.98; premorbid IQ was estimated using the National Adult Reading Test[55] which has been shown to adequately estimate premorbid intelligence in people with dementia[56]) or area-based deprivation (the Scottish Index of Multiple Deprivation;† p=0.39). Therefore people with dementia who have their diagnosis correctly recorded on their death certificate are representative of the general population of people with dementia, at least in terms of intelligence and socioeconomic status.

Another factor might be the extent of the medical history known to the certifying doctor at the death of the patient. If someone is admitted to hospital as an emergency and dies soon afterwards, it may be that a junior doctor who does not know the patient's medical history in detail completes the death certificate. Another person with dementia who remains relatively well and whose death is certified by their GP who knows them well might be more likely to have their diagnosis of dementia correctly recorded. An additional analysis using the LMTC cohort study not included in the published article shows that the survival of people with treated Alzheimer dementia who do not subsequently have dementia correctly recorded on their death certificate is poorer than those who do have dementia recorded (age- and sex-adjusted hazard ratio; 95% confidence interval: 1.76; 1.44, 2.14; Figure 4, p. 13), adding weight to this conjecture.

† SIMD is a measure of small area multiple deprivation encompassing seven domains: income, employment, health, education, skills and training, housing, geographic access to services, and crime. Please see http://www.scotland.gov.uk/Topics/Statistics/SIMD for further information.

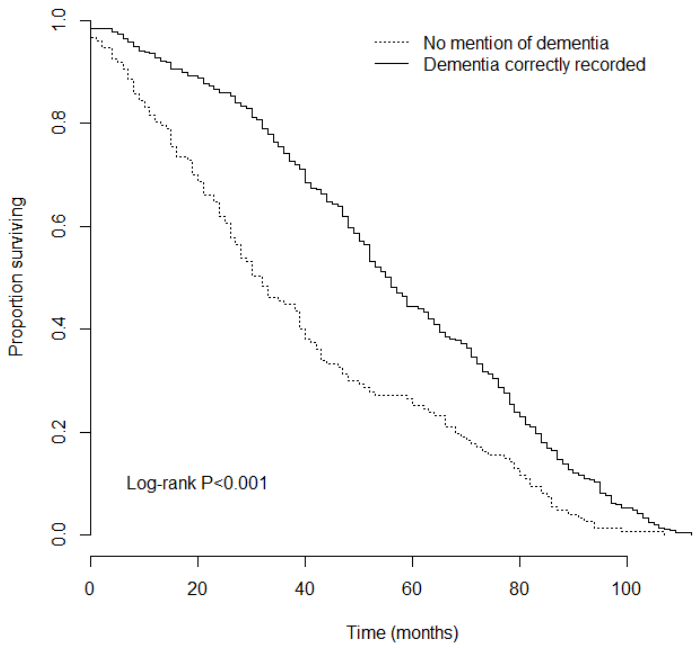


Figure 4. Kaplan-Meier survival plot of the Lothian Memory Treatment Centre cohort study showing better survival in patients with treated probable Alzheimer dementia who had dementia correctly recorded on their death certificate than those who did not have dementia correctly recorded

Since having dementia correctly recorded on a death certificate is associated with better survival, one could infer that it is the fitter people – that is, people with fewer comorbidities – who might be the ones to have their dementia diagnosis correctly recorded on their death certificate. In reality this is an under-researched area and, crucially, there are no published studies comparing the outcome of dementia death compared to incident dementia diagnoses in observational studies.

Studies using linkage to clinical sources of data, in contrast to screening studies of the population, are further subject to the unavoidable problems of underdiagnosis of dementia in the community with approximately half of all people with dementia thought to have been given a diagnosis. Estimates for 2012 are that between 31.9% and 75.4% of the total number of cases of dementia are diagnosed appropriately in the community (64.4% overall in Scotland and 46.0% overall in the UK).[57] A recent study at the Royal Free Hospital found that the prevalence of dementia was 42% of all acute medical admissions of adults over 70 years old but that only half of these had received a formal diagnosis of dementia in the community.[58] This result is corroborated by studies of GP

dementia registers.[59] However the method used to calculate the expected number of people with dementia from which to estimate the proportion who are diagnosed is complicated and this choice is likely to have a substantial effect on the outcome. Connolly et al. (2012)[59] used national prevalence estimates from the MRC Cognitive Function and Ageing Study to estimate their expected numbers of people with dementia.[60] The Scottish Government and Alzheimer Scotland, on the other hand, use the EuroCoDe synthesised estimated prevalence rates.[32]

4. Geographical Variation in Dementia

It can be seen that there are numerous factors complicating the seemingly simple process of comparing disease rates reported in two studies. One could even argue that it is meaningless to compare such studies, given the likely huge methodological differences between them. One way to overcome the majority of these problems is to restrict our attention to within-study comparisons – studies which have used identical methodologies in two or more geographical areas at the same time. This was the approach taken in the systematic review and meta-analysis published in the *International Journal of Epidemiology* in 2012 (article 2).[7]

Since it was not possible to formulate the research question in the familiar form of 'intervention *x* for condition *y*' as in systematic reviews of interventions,[61] a more fluid approach had to be taken, as is common in systematic reviews in the social sciences.[62] Thus the research question was formulated as simply: is there evidence, based on within-study comparisons, of geographical variation in dementia, at any scale? In consultation with an information scientist at the MRC Social and Public Health Sciences Unit, Glasgow, it was decided to make the literature search similarly inclusive. Therefore, in addition to the traditional biomedical databases, we included geographical and international sources, likely to include articles of relevance, as well as theses and grey literature. The intention, given the broad research question, was to capture as many relevant articles as possible for inclusion in the final review.

The wide net that was cast resulted in a very large number of records to be screened by the two reviewers, as described in the article. However, the methodology

used was systematic, rigorous and reproducible. The inclusion criteria used were also inclusive, encompassing any methodology whether cross-sectional or longitudinal (though the final review was stratified into prevalence and incidence studies). Studies of all types of dementia were included, apart from conditions where the dementia either resulted from external causes, for example alcohol or a head injury, or was a late feature of the condition, for example Parkinson's disease. An exception to this latter rule was the Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia complex on Guam.[63, 64] Since this condition, and similar clusters on the Kii peninsula of Japan[65] and in West New Guinea,[66] was a clear example of the phenomenon of interest – disease clustering – it was included by selecting a representative paper from the large number which have been published.

One important challenge in writing this article was the multitude of possible ways of structuring and organising the included studies, each of which made sense and could theoretically be justified.‡ Articles could be reported in chronological order, either according to the dates the studies were conducted or publication date. They could be organised according to geography, perhaps dividing them up by continent – though studies comparing areas in different continents, for example the Ibadan-Indianapolis study[17-20] would be difficult to fit into such a schema. Methodological quality of study would be another candidate, perhaps giving more weight to the more robustly designed and conducted studies. Finally, one could choose to arrange the article by geographical scale of the comparisons made. Since the practical implications of the article in terms of investigating potential reasons why the geographical distribution of dementia might be non-random were most related to the latter approach to organising the included studies, I chose to arrange them according to that criterion into five groups: (1) Comparisons between countries (or studies of a defined area where country of birth was used as a proxy geographical variable); (2) rural-urban comparisons (which included some studies also included in the other groups); (3) comparisons between regions (defined as larger than a town or city but smaller than a country); (4) comparisons between towns or

‡ Foucault (1966/1970)[67] refers to 'a certain Chinese encyclopaedia' which classifies animals into the following categories: '(a) belonging to the Emperor, (b) embalmed, (c) tame, (d) sucking pigs, (e) sirens, (f) fabulous, (g) stray dogs, (h) included in the present classification, (i) frenzied, (j) innumerable, (k) drawn with a very fine camelhair brush, (l) *et cetera*, (m) having just broken the water pitcher, (n) that from a long way off look like flies.' He goes on to suggest that there is no single correct way of classifying things.

cities; and (5) small area comparisons, for example postcode or zipcode areas. With regard to identifying putative risk or protective factors for dementia, it is the last of these – large-scale comparisons – which are potentially the most informative. However, as I note in the article, these are the least studied in the published literature.

I decided, *a priori*, to write a narrative review of comparisons at the various scales mentioned above, with the exception of rural-urban comparisons. I felt that these might be sufficiently homogeneous to lend themselves to quantitative combination in a meta-analysis. This was indeed the case but the distinction between rural and urban areas was by no means uniformly dealt with between studies. In fact, as discussed in the article, the definition of rurality is probably responsible for a large proportion of the heterogeneity in the meta-analyses of prevalence and incidence. Some studies even failed to define what constituted a rural area and what constituted an urban area.

This article was the first review on the topic based on within-study comparisons which, as outlined above, is essential when comparing observational studies and the very first meta-analysis of rural-urban effects on dementia. It has a number of important implications. First, it is a robust attempt to synthesise the literature on geographical variation in dementia taking into account the various methodological difficulties outlined above.

Second, since it shows geographical variation in dementia at all scales, though admittedly not in every study, this leads one to speculate as to what might be responsible for this non-random geographical distribution of disease? It is likely that both genetic and environmental factors are responsible but very few studies have attempted to separate these effects; this systematic review identified only two. A study in Newfoundland which identified a difference in dementia risk in those born on the north side of Bonavista bay compared to the south suggested that genetic relatedness might account for a proportion of the effect by examining the number of surnames in each group.[68] A Scottish study of young-onset Alzheimer disease examined the number of common ancestors in order to estimate case kinship and concluded that familial factors partly contributed to the high incidence of dementia in Lanarkshire.[69]

Third, the article is the first step in a process of hypothesis generation to identify possible risk or protective factors for dementia which might similarly vary with geography. For example, the finding that Alzheimer dementia prevalence and incidence was higher in rural areas than urban areas should prompt questions about what might be the differences between such areas that increase risk in rural areas or reduce it in urban areas. It should be pointed out that not all risk or protective factors for dementia will vary by place – some may have the same effect on individuals regardless of where they are located.

Studying the geography of disease is a powerful route to identifying putative risk factors. The legend of John Snow is being reassessed in the bicentenary of his birth.[70] It has been argued that, in addition to careful recording of data, it was his visualisation of these data (Figure 5, p. 18) which was crucial in identifying the source of the 1854 London cholera epidemic.[71] The substantial impact of the mythical removal of the pump handle is also a lesson to us that simple interventions resulting from careful research can have substantial public health benefits. At the very least, this geographical approach is useful in hypothesis generation. Estimates suggest that delaying the onset of dementia, even by one year, could have substantial effects on the number of people with dementia in the future.[72, 73] With further, more detailed investigation of possible risk factors, it might well lead to advances in understanding of the aetiology of dementia, with potentially important public health implications.

Building on the systematic review of geographical variation in dementia (article 2),[7] I have applied Bayesian disease mapping methodology to two complementary datasets – dementia in Swedish Twins and in the 1932 Scottish Mental Survey cohort (see Appendix C for the manuscript, currently submitted for publication).[8] These studies showed substantial variation in dementia odds – approximately two-fold variation between the south of Sweden (low risk) and the north after removing twin-level random effects (which will approximately correspond to genetic and shared environmental factors). Furthermore, this variation is not observed in Scotland when location at age 11 is used but is in later adult life, suggesting that different factors might have their effects at different points in life. The findings are generally replicated when Alzheimer dementia is used rather than dementia of all types in both studies.

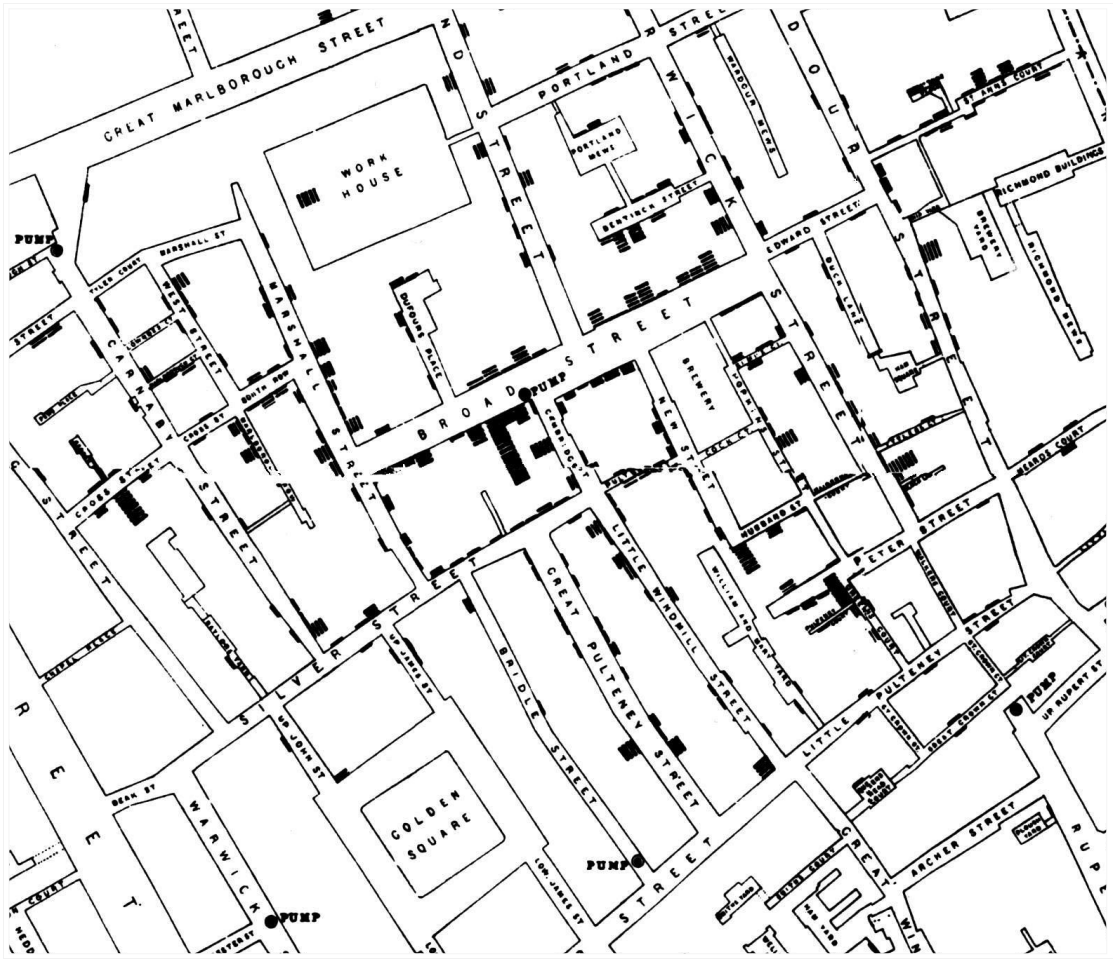


Figure 5. Detail of John Snow's disease map of the 1854 London cholera epidemic with Broad Street and the pump at the centre of the epidemic approximately at the centre of the map. Source: Snow (1855)[74]

At first glance, these models seem to replicate the findings of the systematic review, in that the risk of dementia is greater in the rural north of Sweden and Scotland, at least as far as the Moray Firth. However, if this were the case, one would expect Stockholm to demonstrate a reduced risk of dementia, which is not the case. Similarly, dementia risk in the relatively rural Borders is reduced and in the urban central belt is approximately average, based on adult location. Furthermore, the increased effect of early life rural living seen in the meta-analysis[7] is not borne out in the Scottish study as area of residence in early life does not seem to affect later dementia risk. Nevertheless, both studies confirm non-random variation in dementia rates.

The implications of these findings are that geographical variation in dementia is explained by at least one environmental factor and that, if it could be identified and modified, it would be possible to halve dementia rates. We can infer that this environmental exposure has its effect in late adolescence or adulthood and that, given the pattern of risk seen, it may relate to latitude. It is hoped to continue this work by confirming an environmental effect by including a polygenic risk score for Alzheimer disease as a covariate and also examining the effect of incorporating other potential environmental risk or protective factors into the models to attempt to explain the observed variation. The final aim of this work is to identify potentially modifiable risk factors which could be tested in an interventional study.

5. The Life Course Paradigm in Dementia Epidemiology

In recent decades there has been increasing interest in the life course paradigm in epidemiology,[75] arguably beginning with the Barker hypothesis or 'foetal origins of adult disease.'[76] The life course approach has been defined as the "study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life;"[75] that is, during any period of life from conception to death. Clearly, within such a paradigm, the temporal ordering of exposures is extremely important and it is likely that chronic disease risk could relate to the cumulative effect of risk and protective factors along the life course. In addition to this 'accumulation of risk,' the other main conceptual life model is the 'critical period model,' which suggests that exposures at a particular point in life might have a crucial effect on later disease risk. If the exposure only has its effect on disease risk during a particular period, this is said to be a 'critical period.' However if the exposure is likely to have some effect at any point in life but that a particular period is associated with additional sensitivity to this effect, such a period of time is referred to as a 'sensitive period.'

The life course paradigm has also been applied in dementia epidemiology and it is likely that factors at all stages of life affect dementia risk.[77] This model is supported by neuropathological evidence suggesting that the pathogenesis of Alzheimer disease might begin decades before the disease becomes clinically manifest.[78-80] However, the failure of numerous trials of disease-modifying treatments for Alzheimer disease[81] implies that we

still do not properly understand the pathophysiology of dementia. Such discoveries might shed light on the disease processes resulting in dementia but, in their absence, current clinical practice remains focussed on treating individuals after they have become symptomatic.

This strategy has not been successful in terms of therapeutic discoveries.[82] Indeed, there have been recent calls for a wholesale change of approach and the life course paradigm could be a useful model to guide future research. This clearly means that intervention would be necessary before the clinical onset of dementia. However, the obvious difficulty is that, in the absence of any symptoms, there are currently no reliable methods to identify if an individual will go on to develop dementia. There are biomarkers available for a number of the pathological processes associated with Alzheimer disease – primarily amyloid or tau – which are hypothesised to change at various times before dementia can be clinically diagnosed (Figure 6, p. 21) but no robust link has been shown between one or more biomarkers and later developing Alzheimer dementia. Work is currently underway to formalise this conceptual process[83] and validate these proposed biomarkers in terms of quality control[84] and diagnostic test accuracy[85, 86] but we are still not in the position where Alzheimer disease can be confidently identified in asymptomatic individuals. The exception is carriers of familial mutations who can be identified by their genotype. However, until accurate preclinical diagnosis is possible, there is an urgent need to focus instead on prevention at a population level.

We have already seen that a small delay in dementia onset could have a dramatic effect on the number of people with the condition.[72, 73] Thus modification of risk factors to prevent dementia might have a substantial impact on disease rates. Given the findings mentioned above regarding the long preclinical course of Alzheimer disease, at least, later life is probably not the best time to attempt to modify dementia risk; it might be necessary to begin intervening in mid-life or even earlier.[88]

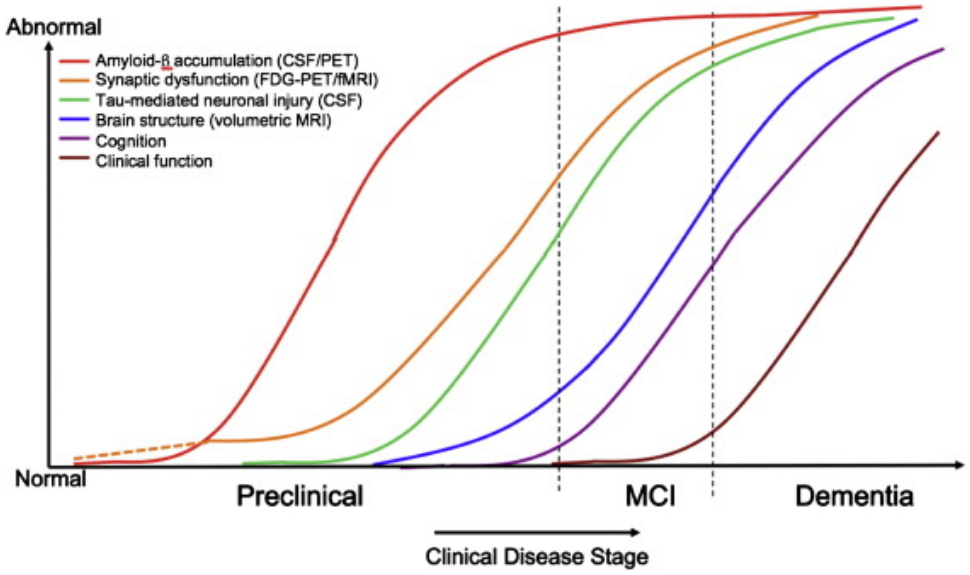


Figure 6. Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (*y*-axis) as a function of disease stage (*x*-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Source (figure and rubric): Sperling et al. (2011)[87]

Corroboration of this need for intervention sufficiently early in life comes from systematic reviews of trial evidence that neither lowering serum cholesterol with statins[89] or lowering blood pressure[90] in later life has any beneficial effect on dementia risk. There are no aetiological trials of the effects of modifying cardiovascular disease risk factors in mid-life. However, there are observational data which suggest that there is an association between high mid-life total cholesterol,[91, 92] obesity,[93] and hypertension,[92] though there was a suggestion that treatment for hypertension might influence this association.[94] There is also some evidence, again based on observational data, that individual cardiovascular disease risk factors might have a more complex relationship with dementia when more than one is present.[92] It is possible that these associations between mid-life cardiovascular disease risk factors and dementia might be due to confounding. However, it is also a possibility that modification of these risk factors sufficiently early in life could have a beneficial effect on dementia risk, even if

modification in later life does not.[88] I am currently working on an observational study exploring these associations, described below.[95] Looking even earlier in life, there are currently no studies directly linking prenatal factors with dementia risk but birth parameters are associated with cognitive function at age 11[96, 97] (which is a risk factor for later dementia[98, 99]), cognitive ability in later life,[100] and late-life white matter integrity.[101]

All of this evidence leads one to conclude that there is almost certainly a state when an individual has Alzheimer *disease* but not yet Alzheimer *dementia*. Indeed, as alluded to above, the most recent diagnostic criteria for Alzheimer dementia acknowledge this and attempt to conceive of states before Alzheimer dementia could be diagnosed including MCI, when minor symptoms are present but not sufficient to merit a diagnosis of dementia, and 'preclinical AD' when Alzheimer disease is hypothesised to be present without manifest dementia.[40, 87, 102]

The life course paradigm and the early inception of Alzheimer *disease* suggest that merely thinking in terms of 'midlife' risk factors may not be sufficiently complex to do justice to the processes throughout the life course which result in an individual developing dementia.[77, 103-108] However, the question of appropriate methodologies for investigating public health initiatives modifying midlife risk factors is not a straightforward one. First, observational data can only demonstrate an association and do not prove causality (Bradford Hill's criteria for a causal association comprise strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy[109]). Second, if one is to rely on dementia mortality data, as many of the papers included in this thesis do, this would require extremely long periods of follow up following an intervention in order to allow sufficient numbers of people to die with dementia. Thus, ideally a proxy endpoint should be used in such studies. The clinical onset of dementia would be better than dementia mortality, but would still require extended follow up. Cognitive decline could also be used, as has been the case in a number of studies, but this is only an element of dementia and it is unclear how risk factors for cognitive decline might relate to dementia. Further work on biomarkers for Alzheimer disease and other dementias might mean that these outcomes could be used in intervention studies years, or even decades, before the clinical onset of dementia.

However, at the moment, no biomarkers have sufficient predictive validity, either alone or in combination, for this use.

The remainder of this thesis will be devoted to summarising the work represented by articles 3-6[9-12] investigating risk factors for dementia and further research building on them. While some of this work may not fit within the classical life course paradigm, this approach, summarised above, has informed much of the thinking surrounding these analyses and much of my planned, future work, outlined below.

6. Risk Factors for Dementia

As mentioned above, record linkage provides a powerful methodology for observational studies. This section of the thesis outlines a number of articles examining potential risk factors for dementia and cardiovascular disease (which partially shares aetiology with dementia) using the Health Survey for England[110] (HSE) cohort studies from 1994-2004. Passive follow up (through linkage to NHS mortality registries) until the first quarter of 2008 turns these cross-sectional studies into longitudinal, prospective cohort studies. Through the combination of multiple studies, it is possible to have very large sample sizes. This allows one to examine the exposure-outcome association in detail, including conducting gender-specific analyses, examining the shape of the association (for example whether there is a linear dose-response relationship or if there is a threshold effect), and detailed investigation of alternative explanations for the observed association, including reverse causality.

6.1. Cardiovascular disease risk factors

The evidence for and against an association between cardiovascular disease risk factors and dementia has already been mentioned above. Article 3 investigated the possibility that a risk score comprising multiple cardiovascular disease risk factors, widely used in clinical practice – the Framingham cardiovascular disease risk score – might also have predictive utility in dementia.[9] Since these conditions may partially share aetiological factors, this seems a reasonable hypothesis and could have substantial implications for public health and clinical practice. However, as the article and the results summarised in Figure 7 (p. 24) show, the large predictive utility of the risk score (a 10% increase in the

score is associated with a four-fold increase in the risk of dementia) is entirely explained by the age component. This merely reiterates the well-known fact that the greatest risk factor for dementia is age. However, Figure 7 also shows that the same could almost be said for cardiovascular disease itself – as is mentioned in the article, age explained 88% of the ability of the Framingham cardiovascular disease risk score to predict cardiovascular disease.

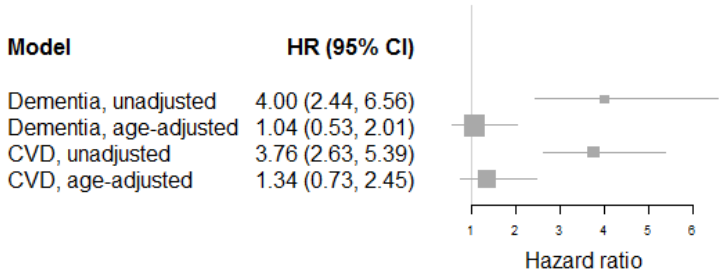


Figure 7. Hazard ratios (with accompanying 95% confidence intervals) for the association between a 10% increase in the Framingham Cardiovascular Disease (CVD) Risk Score and dementia and CVD. Unadjusted models as well as age-adjusted models are shown. Summary of results from article 3[9]

However, as alluded to above, the Framingham cardiovascular disease risk score comprises multiple risk factors: age, sex, systolic blood pressure, smoking, diabetes, total serum cholesterol, and serum HDL cholesterol (BMI can be substituted for the last two variables in an alternative version of the risk score which does not require blood to be drawn).[111] While age accounts for the majority of the value of the Framingham cardiovascular disease risk score, it would be interesting to know the relative contributions of the other cardiovascular disease risk factors which make it up. Due to the short report format, it was not possible to describe this in article 3. Figure 8 shows a more recent piece of work, currently under review, which compares the association between individual risk factors and dementia and cardiovascular disease death.[112] This study uses an updated dataset with linkage until the first quarter of 2011 providing longer follow up than in the dataset used in articles 3-6.[9-12] It also includes a larger number of cohort studies, including the Scottish Health Survey[113] (SHS) as well as the HSE. Thus this larger analysis was able to include data from ten cohort studies – the HSE 1998, 1999, 2003-6, and 2008 and the SHS 1995, 1998, and 2003 – comprising

103,764 men and women with a mean follow up of 7.9 years compared to 7.1 years in article 3.[9]

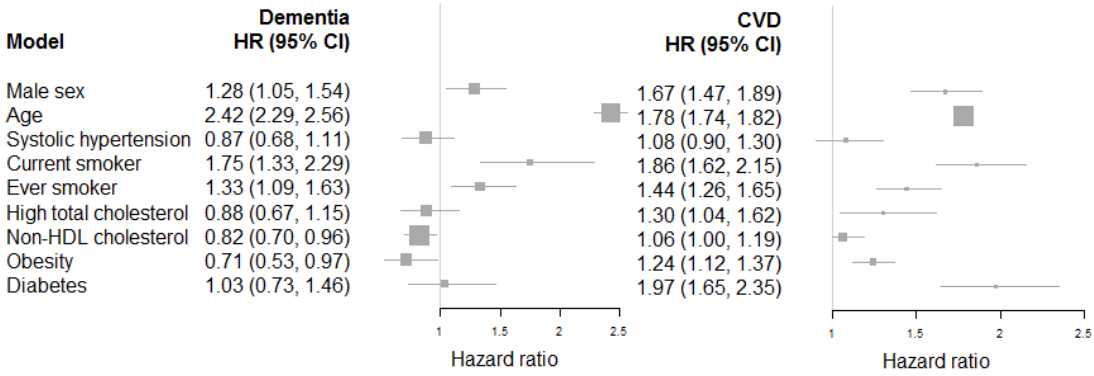
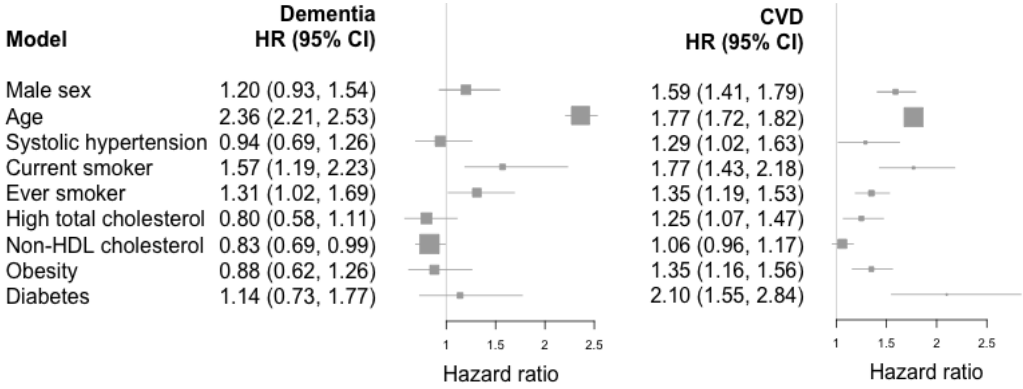


Figure 8a. Hazard ratios (HR with accompanying 95% confidence intervals) for the association between individual cardiovascular disease (CVD) risk factors (components of the Framingham CVD risk score[111]) and dementia and CVD death



8b. HR (with accompanying 95% confidence intervals) for the association between individual CVD risk factors (components of the Framingham CVD risk score[111]) and dementia and CVD death with deaths occurring in the first five years of follow up dropped

HR for age is per five-year increase. Systolic hypertension is defined as systolic blood pressure ≥140 mmHg. Current smokers are compared to ex- or never-smokers. Ever smokers comprise current or ex-smokers and are compared to never smokers. High total serum cholesterol was defined as > 6.2 mmol/L or on lipid-lowering treatment. Non-HDL cholesterol was calculated by subtraction of HDL-C from total cholesterol, yielding a measure that encompasses low-, intermediate-, and very-low-density lipoprotein cholesterol; HRs are per standard deviation increase (disadvantage; one SD = 1.2 mmol/L). Obesity is defined as BMI ≥30 kg/m^2 (underweight participants – BMI <18.5 kg/m^2 – not included in this model). Diabetes was identified from a complex diabetes indicator comprising doctor-diagnosed diabetes, longstanding illness (diabetes), HbA1c, and diabetes medication

Source: These data are reported in an article which is currently submitted for publication[112]

In fact, while age and smoking are clearly associated with later dementia-related death (Figure 8a, p. 25), the status of other cardiovascular disease risk factors in relation to dementia death is less robust, particularly when deaths occurring in the first five years of follow up are excluded – a technique to investigate the possibility of reverse causality – as shown in Figure 8b (p. 25). The parallel results for cardiovascular disease-related death are shown on the right hand side of Figures 8a and 8b. These give us confidence in the dementia findings since they confirm the expected association between all of the cardiovascular disease risk factors, apart from non-HDL cholesterol, and cardiovascular disease mortality. Thus the relationship between cardiovascular disease risk factors and dementia, which has received a great deal of research attention,[114] may not be such a fruitful avenue towards the prevention of dementia as has been previously thought.

6.2. Psychological distress

The above analyses of the association between cardiovascular disease risk factors and dementia suggest that 'traditional' risk factors may not be as clearly associated with dementia as has been previously thought. Therefore, the net for putative risk factors must be cast wider and more novel risk factors sought. One such risk factor, examined in articles 4 and 5, is psychological distress.[10, 11] In these articles, the 12-item General Health Questionnaire[115-117] (GHQ-12) was used as the measure of psychological distress, with one point scored for each answer to an item denoting distress, giving a score from zero to 12.[§] These analyses involved ten of the HSE cohort studies (the GHQ-12 was not administered in 1996) and the two papers used different methodologies, reflecting my learning of new statistical techniques. In article 4 the data from all ten studies were simply pooled together and overall Cox proportional hazards models[118] were calculated.[10] However, it is unlikely that this methodology adequately allows for within-study clustering and therefore the more sophisticated individual participant meta-analysis (IPMA)[119] was used in subsequent studies.[11] These two methodologies are compared below as well as an empirical comparison of their effect on the observed association between psychological distress and dementia death (p. 30).

[§] Have you recently: 1. Been able to concentrate on whatever you are doing? 2. Lost much sleep over worry? 3. Felt that you are playing a useful part in things? 4. Felt capable of making decisions about things 5. Felt constantly under strain? 6. Felt you couldn't overcome your difficulties? 7. Been able to enjoy your normal day to day activities? 8. Been able to face up to your problems? 9. Been feeling unhappy and depressed? 10. Been losing confidence in yourself? 11. Been thinking of yourself as a worthless person? 12. Been feeling reasonably happy, all things considered?

IPMA aggregates results from a number of different studies, in the same way as a traditional literature-based meta-analysis, but offers a number of advantages over the latter. Potential advantages outlined by Riley et al. (2010)[119] include consistent inclusion and exclusion criteria, statistical analysis can be standardised for all studies, a variety of baseline characteristics may be incorporated into models – including multiple risk factors at once, sensitivity and subgroup analyses are possible, and a more sophisticated approach to missing data can be used. Other advantages of the IPMA methodology are outlined in the introduction to article 5.[11]

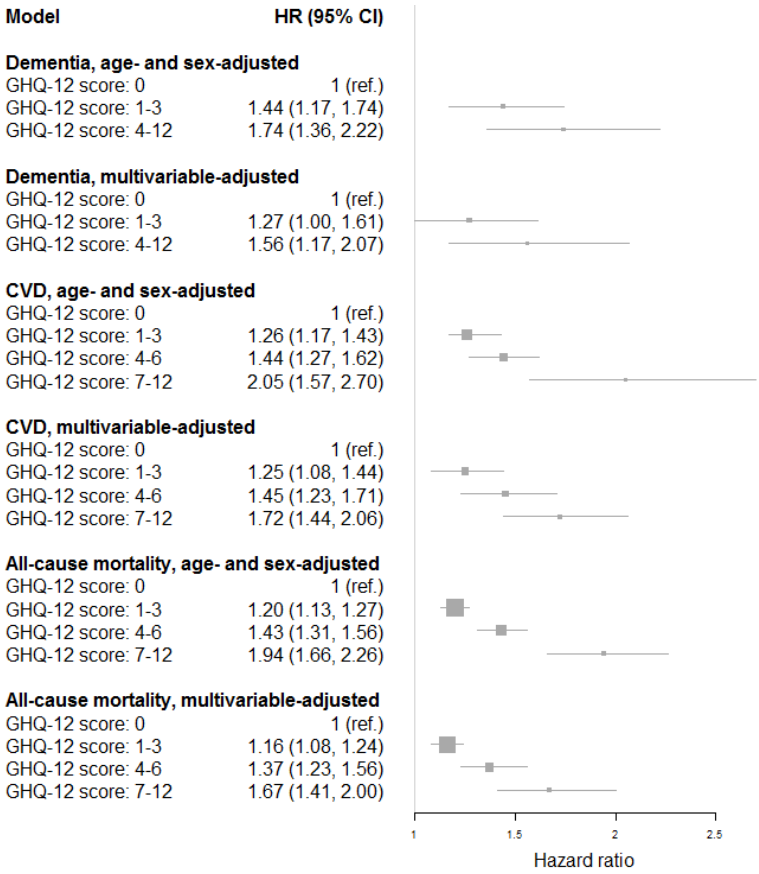


Figure 9. Hazard ratios (with accompanying 95% confidence intervals) for the association between psychological distress (as measured by the 12-item General Health Questionnaire) and dementia death, cardiovascular disease (CVD) death, and all-cause mortality. Age- and sex-adjusted models as well as multivariable-adjusted models are shown. Summary of results from articles 4 and 5[10, 11]

These are the first IPMAs in the field of dementia research (though not the first in the area of mental health[120]) and also the first IPMAs in any field with a psychological (article 5)[11] or a socioeconomic (article 6)[12] exposure. A convenience sample of the HSE

cohort studies was used, since one purpose of these studies was proof of concept, as the fact that the HSE studies are methodologically very similar reduces the between-study heterogeneity. Results from articles 4 and 5 are summarised in Figure 9 (p. 27).[10, 11] Briefly, there was a dose-response association between psychological distress and all-cause mortality, as well as mortality from cardiovascular disease and dementia. There was an increased mortality seen even at very low levels of distress, lower than the cut off used in most epidemiological studies (i.e. scores of one, two, or three) compared to those with no psychological distress. The IPMAs were conducted using the statistical language R,[121] and example syntax for running such analyses is given in Appendix D.

6.3. Socioeconomic status

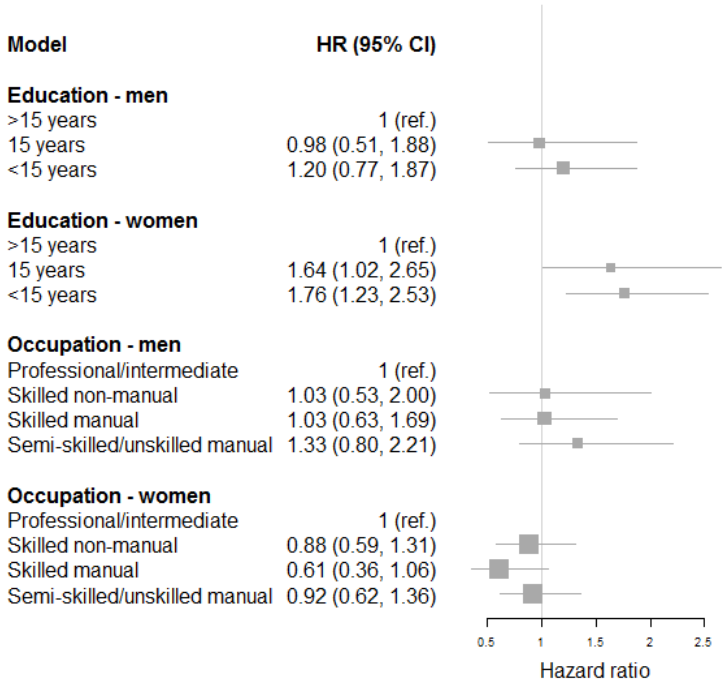


Figure 10. Multivariable-adjusted hazard ratios (with accompanying 95% confidence intervals) for the association between age upon leaving full time education (Education) and occupational social class (Occupation) and dementia death in men and women. Summary of results from article 6[12]

The final risk factor to be examined is socioeconomic status, a complex, multi-faceted entity which is particularly amenable to study from a life course perspective as it is likely to change during an individual's life. In article 6 ("Socioeconomic Status as a Risk Factor for Dementia Death: An Individual Participant meta-analysis of 86 508 Men and

Women from the United Kingdom")[12] it is captured as age upon leaving full-time education and adult occupational social class, measures which relate to different periods of life, albeit with the former being based on distant recall of the age upon leaving school. Thus they offer some insight into the association between socioeconomic status in early and mid-life and later dementia death. Early life factors, in particular, are an element of the life course approach, even if this analysis does completely not fit into the paradigm, if strictly defined. The results from article 6 are summarised in Figure 10 (p. 28).[12]

The only positive association is between educational attainment and dementia death in women. Additionally, since we are able to incorporate adult occupational social class into the model we can show that this association is not mediated by adult socioeconomic status. Therefore there is something about education which influences dementia risk, possibly to a greater extent in women than men – though this gender difference might relate to statistical power. Given the limitations of the models it is difficult to comment further on the life course effects of socioeconomic status on dementia, but it would seem that an accumulation of risk model does not fit this association well. It might be that there is rather a critical or sensitive period for exposure to socioeconomic deprivation. Education may influence cognitive reserve[122-124] which is hypothesised to relate to the extent to which impaired brain function can be tolerated without producing overt symptoms. More recently it has been shown that educational attainment is partially genetically determined[125] which further complicates the interpretation of these findings.

6.4. Strengths and limitations of these studies

The relative strengths and limitations of these studies are considered in each article but an attempt will be made to consider these in more detail here. The generalizability of the results is likely to be high since these are general population samples. However, this requires some clarification since, as is the case in all sample-based research, the people who participate in studies are unlikely to be identical to the general population out in the real world. Research participants tend to be healthier than average and this indeed turns out to be the case in relation to the HSE and SHS surveys. In another analysis using the same cohort studies it has been shown using negative binomial regression that all-cause

mortality in the cohort studies is 31% lower in HSE and 21% lower in SHS than the general population in each country, based on Office for National Statistics mortality data.[44]

There are a number of things, with the benefit of hindsight – particularly in article 4 – which could have been done better. The later papers are methodologically sounder, using IPMA to take account of between-study heterogeneity, and it would have been better to use this approach in the psychological distress-dementia analysis. Table 1 shows a comparison of simple pooling and IPMA on the association between psychological distress and dementia death using the updated HSE and SHS dataset. It can be seen that using IPMA does not alter the conclusions drawn from an analysis using simple pooling but that the effect estimate is slightly attenuated using pooling. The heterogeneity of the association in each study has been highlighted (for example, see Figure 2 from Article 5, p. 100) even though the surveys use very comparable methodologies from year to year. If a similar analysis were conducted using a number of less similar, more heterogeneous datasets, it might be that the difference between simple pooling and IPMA would be even more marked.

Table 1. Comparison of simple pooling and IPMA techniques on the association between psychological distress and dementia death: the Health Survey for England 1994, 1995, 1997-2006, 2008 and the Scottish Health Survey 1995, 1998, and 2003

			GHQ-12 score		
	N	**Dementia deaths**	**0 HR**	**1-3 HR (95% CI)**	**4-12 HR (95% CI)**
Age- and sex-adjusted					
Pooling	166632	1049	1 (Ref.)	1.44 (1.26, 1.65)	1.72 (1.46, 2.02)
IPMA	166632	1049	1	1.45 (1.26, 1.67)	1.75 (1.48, 2.07)
Multivariable-adjusted[1]					
Pooling	156974	986	1	1.39 (1.20, 1.60)	1.59 (1.33, 1.89)
IPMA	156974	986	1	1.40 (1.21, 1.62)	1.62 (1.35, 1.94)

[1] Models adjusted for age, sex, occupational social class, age upon leaving full-time education, smoking status, frequency of alcohol consumption, diabetes, and longstanding illness

Furthermore, slightly different measures of socioeconomic status were used in this paper compared to later analyses. Three measures of socioeconomic status were used in article 4: individual occupational social class, head of household occupational social class (referred to as parental occupational social class in the article), and educational attainment (age upon leaving full-time education). It was later felt that this amounted to over-adjustment and subsequent analyses used only individual occupational social class and educational attainment as measures of socioeconomic status.

However, the two major criticisms which can be levelled against all the analytic papers (articles 2-6) are (a) confounding and (b) the question of whether dementia mortality is a valid outcome for epidemiological research. Related to the former is the question of biological plausibility of the observed associations, which is one of Bradford Hill's criteria for causation.[109] In article 2,[10] examining the association between psychological distress and dementia death, the possibility that this association could be mediated by cortisol was mooted – affective disorders are associated with hypercholesterolaemia which has been shown to be toxic to the hippocampus.[126] However, there are alternative possibilities, including reverse causality – as discussed in the article – or mediation by the identified association between psychological distress and cardiovascular disease,[11] given the possibility of overlapping aetiology of the two conditions. Thanks to the detailed assessments of the HSE participants at baseline, we were able to incorporate a large number of important potential confounders into our models, including cardiovascular disease risk factors, diabetes, risk behaviours such as smoking and alcohol use, educational attainment, and occupational social class. Many of these risk factors are not independent and may vary throughout life. Therefore, it may be that simply measuring them at a single point in time and incorporating them into Cox models might not adequately reflect the complexity of these exposures throughout the lifecourse. Notwithstanding these caveats, none of these factors had a substantial effect on the observed association, suggesting that they do not explain the association. Nevertheless, the possibility of residual confounding remains.

Given the low levels of dementia diagnosis in the community and the low – but improving – levels of recording of dementia on death certificates, it is essential to

consider whether it is valid to use dementia mortality as an outcome. In terms of cardiac disease, the only UK study comparing death certification with approximately 60 autopsy findings[127] found correct recording on death certificates in all 21 cases examined. Elsewhere, in Norway, analyses of 1140 autopsies revealed that death certification of CVD is satisfactory for the purposes of epidemiological research.[128] No such work has been published for dementia outcomes, but one could speculate that mortality reporting may be a less accurate marker of actual dementia pathology than is the case for cardiovascular disease, for example. This is partly due to the lack of clear correspondence between pathology and symptoms – the disconnect between Alzheimer *disease* and Alzheimer *dementia*, mentioned above. This disconnect may relate to cognitive reserve, in that individuals with higher cognitive reserve are likely to develop fewer symptoms for a given level of pathology.[122] Another reason why clinical dementia might less perfectly correspond to pathology is the fact that, as alluded to above, a diagnosis of dementia in life is almost never more certain than 'probable' and the correlation between clinical and neuropathological diagnoses is less than perfect.[129]

There are no studies comparing the results of an individual analysis using dementia mortality and incident cases as outcomes. Until this is the case, it will be very difficult to make a definitive decision whether dementia mortality is an adequate outcome for observational research. However, it is encouraging that dementia mortality reporting is improving and almost three quarters of people with Alzheimer dementia had dementia correctly recorded on their death certificates in article 2.[6] Thus, dementia mortality reporting is not perfect but it is likely to be an adequate outcome for the purposes of observational research.

Of course, dementia is not a single entity, but rather a complex of conditions all of which result in the dementia syndrome. Alzheimer disease is the most common disease causing dementia, followed by vascular dementia, dementia with Lewy bodies, fronto-temporal lobar degeneration, and alcohol-related brain damage.[130, 131] This heterogeneous group of diseases is unlikely to have identical aetiologies and so it would be ideal to examine each condition separately, particularly when there is such an urgent need to identify modifiable risk or protective factors. Unfortunately, in the present analyses, we were restricted to the non-specific category of 'dementia' which is a

substantial limitation. While reporting of dementia on death certificates is likely to be adequate, use of non-specific diagnostic codes is common so that reporting of specific dementia sub-types is likely to be much less reliable than dementia reporting overall. Using sub-type specific diagnoses would result in a very small number of disease events, greatly reducing the statistical power of the analyses, as well as the robustness of these diagnoses being questionable. Thus, while large-scale epidemiological studies using dementia death as an outcome are a useful place to start, much more detailed work looking at similarities and differences between robustly diagnosed dementia subtypes would be necessary before an intervention could be implemented at a population level.

Dementia mortality data clearly have value in studying the epidemiology of dementia. However, more detailed information including markers for pre-dementia syndromes (cf. Figure 6,[87] p. 21), the timing of onset of clinical symptoms, the point of diagnosis, and subsequent survival would be much more useful. However, dementia sub-type matters here too: the pre-dementia stage of Alzheimer disease is likely to be very different to the pre-diagnostic stages of vascular dementia, dementia with Lewy bodies, or fronto-temporal lobar degeneration.

Only one study was able to consider a risk factor from early life, and then it was based on adult recall of early life experience – age upon leaving full-time education. This distant recall raises concern regarding reporting bias.[132] It would have been useful to have had more risk factors measured early in life, to reduce the possibility of reverse causality which, since the pathological processes of dementia are likely to begin so long before the clinical onset of symptoms, is a substantial challenge in dementia research. Thus, only this study was able to approach dementia from a life course perspective – and then only in the case of socioeconomic status.[12] Even then, the simple Cox proportional hazards models[118] did not explicitly take into account the timing of the measurement of these risk factors and, when further work on life course risk factors is used, it may be necessary to use alternative, more sophisticated methods, such as structural equation modelling.

Indeed this was the only occasion in any of these analyses when a risk factor was measured on more than one occasion. Risk behaviours are likely to alter over the course of an individual's life and many risk factors – such as blood pressure, psychological distress, etc. – may fluctuate over much shorter periods of time. Furthermore, for some potential risk factors (though not those examined in the present analyses, for example cortisol levels) may have a relatively predictable diurnal or other pattern of variation, which would mean that the time of measurement of that particular risk factor is of importance. Similarly the order of measurement of particular factors in a battery of testing may also affect the results, for example measuring an individual's blood pressure immediately after testing their cognition might yield unexpectedly elevated readings.

Furthermore, the risk factors chosen in these articles were dictated by what had been used in the HSE. Thus, the 12-item General Health Questionnaire was used as the measure of psychological distress, since it had been administered in ten surveys, giving a large total sample size. This instrument is widely used in epidemiological research but its relationship with clinical anxiety and depression, or even symptoms of these conditions is unclear. Thus extrapolating conclusions from articles 4 and 5 to clinical populations is complicated.

These articles also include no investigation of transgenerational, or indeed genetic, risk factors for dementia. The former would need datasets where the relationship between at least two generations of participants was known and would need substantial follow up to allow the younger generation to become sufficiently old to be at risk of developing dementia. The latter is a more practical approach and a new and interesting methodology of creating a polygenic risk score for Alzheimer disease[133] for use as a covariate in analyses is becoming feasible in large-scale studies.

7. Planned Future Work

Investigating risk factors from early life often relies on distant recall. An alternative to this is to use parameters which are affected by experiences throughout development but which remain relatively stable thereafter. One such characteristic is height which develops over the first two decades of life. Regarded as a marker of early life illness,

adversity, nutrition or psychosocial stress,[134] while there may be some loss of height in late life, it remains relatively stable from early to late adulthood. Therefore height may capture important environmental characteristics that act during brain development which may then influence dementia risk.[99] Additionally, height is readily and commonly measured, leading to the possibility of large sample sizes. Further analyses, using the updated HSE and SHS datasets, have been conducted examining the association between height and later dementia death and show a dose-response association between shorter stature and risk of dementia-related death.[135]

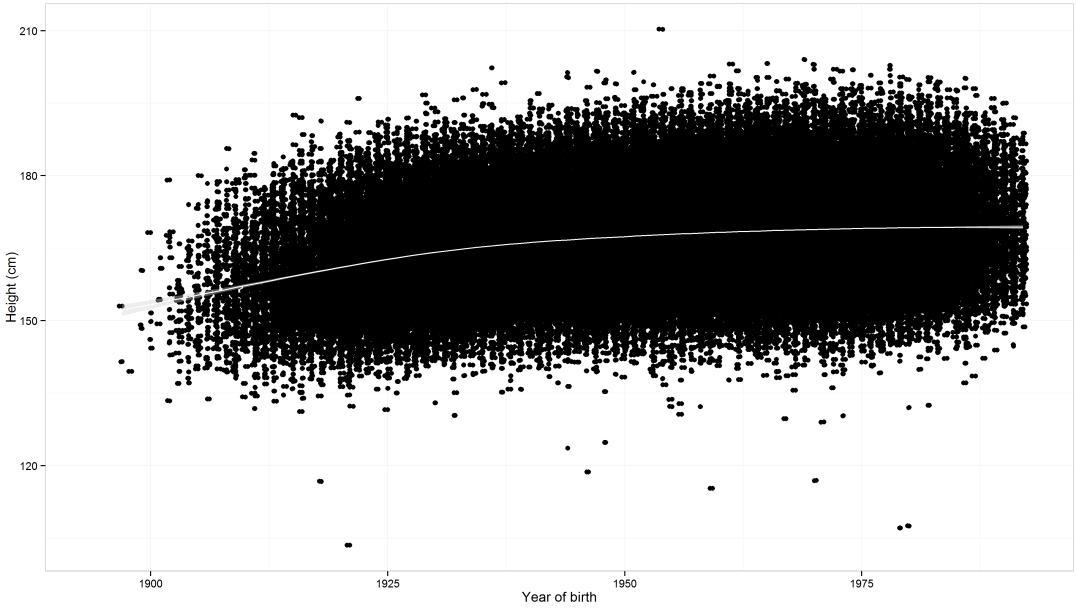


Figure 11. Scatterplot showing the secular trend (with 95% confidence interval) in height by birth year: individual participant meta-analysis of eighteen cohort studies from the Health Survey for England and the Scottish Health Survey (N = 181,800). Source: Russ et al. (Submitted)[135]

Average height has generally increased in a secular fashion over the last hundred years, with particularly marked increase in the first quarter of the twentieth century (Figure 11). The fact that there has been a general improvement of early life circumstances over this period further supports the hypothesis that height captures something of early life experience relevant to later dementia risk. If the height-dementia association did indeed result from improved early life conditions, it might be that the projected increases in dementia prevalence are overestimates, since they do not take

account of secular changes in height. Therefore in the UK, at least, the forecasted increases in dementia prevalence could be overestimated.

Another measurable parameter which captures the effects of exposures over a large proportion of the life course is pulmonary function (Figure 12). Illness and exposure to smoking and pollution throughout life affect lung function and forced expiratory volume in one second (FEV_1) has been shown to be a predictor of mortality.[136] Spirometry is available from six of the HSE and SHS cohort studies and is the focus of a further analysis which is currently under review. This study shows a dose-response association between decreasing pulmonary function and later dementia-related death.[137]

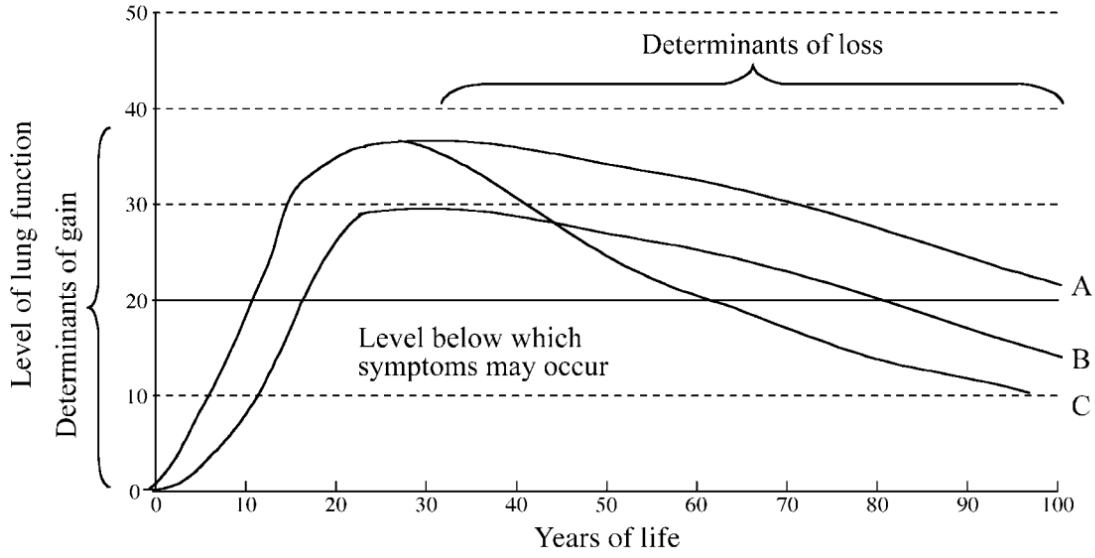


Figure 12. Relative importance of exposures acting across different life course time windows in terms of the natural history of lung function. A = normal development and decline; B = exposure in early life reducing lung function potential; C = exposure acting in mid to later life accelerating age-related decline. Source (figure and rubric): Ben-Shlomo & Kuh (2002)[75]

Further plans include work building on the analyses of cardiovascular disease risk factors[9, 112] by an analysis of the association between such risk factors measured early in life – for example in medical examinations at the start of University attendance – and later dementia death, again identified through record linkage. The advantage to such a study would be that reverse causality would be an unlikely explanation for any

association which might be observed since the baseline measurements would have been collected even before the initial pathological changes associated with dementia might have begun. Such linked datasets exist and an examination of this association is underway.[95]

Further research, building on the epidemiological work outlined here, might also include using alternative methodologies to confirm the associations identified from population-based studies, providing further evidence for causality. This might take the form of animal studies or *in vitro* work to establish the biological plausibility of the association. Once plausible risk factors have been identified, intervention studies would be required before large-scale modification of these factors at a population level could be considered. However, the difficulties associated with midlife intervention studies in dementia have already been considered. Thus, either a proxy outcome, perhaps in the form of one or more biomarkers for Alzheimer disease (or another dementia subtype) could be used. However, until we have identified sufficiently accurate biomarkers, approaches such as Mendelian Randomisation could offer an alternative to traditional intervention studies, such as randomised, controlled trials, allowing us to investigate modifiable environmental risk factors for dementia.[138]

The study in Appendix C suggests that if the modifiable risk factors for dementia could be identified and optimised, dementia rates could be halved.[8] However, the traditional epidemiological work presented in this thesis suggests that we have yet to identify these risk factors, though psychological distress and education may relate to dementia risk. The relationship between dementia and cardiovascular disease is complicated but it may be that population measures to improve cardiovascular disease risk have resulted in the recently observed decrease in dementia rates.[13-15] Another possible candidate suggested by the findings from the Swedish study[8] is sunlight exposure and vitamin D which has been linked to cognition.[139]

8. Conclusions

This thesis has approached the investigation of risk (or protective) factors for dementia from a number of angles and attempted to synthesise these into an integrated approach. Non-random geographical variation in dementia has been highlighted as a fruitful avenue for identifying potentially modifiable risk factors for dementia and I hope to pursue this line of work in the future. More traditional epidemiology has been used to examine possible risk factors using cross-sectional surveys converted to longitudinal cohort studies through linkage with mortality registries. The challenges of combining multiple studies have also been discussed and the advantages of IPMA over simple pooling highlighted. There is much left to be done and current plans of how I intend to build on the published work have also been outlined.

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Appendix A

Publications Submitted for
PhD by Research Publications

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Cognitive and behavioural predictors of survival in Alzheimer disease: results from a sample of treated patients in a tertiary-referral memory clinic

Tom C. Russ[1,2,3], G. David Batty[3,4] and John M. Starr[1,2,3,5]

[1]Scottish Dementia Clinical Research Network, NHS Scotland, UK
[2]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK
[3]Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK
[4]Department of Epidemiology and Public Health, University College, London, UK
[5]NHS Lothian, UK
Correspondence to: Tom C. Russ, E-mail: tom.russ@nhs.net

Objective: This study examined the influence of cognitive and non-cognitive factors at the time of diagnosis on the survival of patients with treated probable Alzheimer Disease (AD).

Methods: Consecutive patients seen at a regional, tertiary-referral clinic completed a battery of cognitive tests and assessments of activities of daily living and neuropsychiatric symptoms. These clinic data were linked with death certificate data for all individuals and survival from diagnosis was calculated. Cox regression models were constructed using the baseline covariates.

Results: The sample comprised 653 patients (459 women), mean age 77.1 years (SD 7.6, range 48–94 years), diagnosed with probable AD and treated with a cholinesterase inhibitor. In the survival analysis, age was a consistently significant predictor of survival with a gender-adjusted hazard ratio of 1.35 (95% CI 1.23, 1.48) for one standard deviation increase in age. Men were at greater risk of death than women (age-adjusted HR 1.44, 95% CI 1.19, 1.73). In a model adjusted for all study variables, Paired-Associate Learning (Cambridge Automated Neuropsychological Test Assessment Battery) and the psychotic factor of the Neuropsychiatric Inventory were significant predictors of survival.

Conclusions: At diagnosis, in addition to the anticipated impact of age and gender, the presence of psychotic symptoms and poor performance on paired-associate learning are also indicators of poor prognosis.

Key words: survival; prognosis; Alzheimer disease; cognitive factors; neuropsychiatric symptoms; cause of death
History: Received 30 March 2011; Accepted 8 August 2011; Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/gps.2795

Introduction

The notion that capturing a series of patient characteristics will aid in estimating prognosis is appealing for clinicians, patients and their relatives as they plan their future. With the number of cases of dementia increasing rapidly (Ferri, *et al.* 2005), there is an obvious need to understand prognosis in people with this condition. Although it is known that mortality in dementia increases with the severity of disease (e.g. Andersen *et al.* 2010), there is a general paucity of data about other predictors of survival and conclusions are limited by the difficulties in extrapolating from populations to individuals. Apart from the more general effect of delirium on survival in all patients (Inouye, *et al.* 1993), comorbid medical conditions (Van Dijk, *et al.* 1996)—particularly cerebrovascular and respiratory diseases (Helmer, *et al.* 2001; Hicks, *et al.* 2010) but also falls, diabetes and cardiovascular disease (Larson, *et al.* 2004; Mielke, *et al.*

2007)—and socio-economic factors, such as education (Musicco, *et al.* 2009) have been shown to affect survival in dementia. Further potential candidates for predictors of survival in people with dementia have included baseline cognitive function (Landi, *et al.* 1999; Andersen *et al.* 2010; Hötte, *et al.* 2010), pre-morbid cognitive ability (cognitive reserve; Stern, *et al.* 1999; Scarmeas, *et al.* 2006), difficulties with activities of daily living (ADLs; Agüero-Torres, *et al.* 1998; Newcomer, *et al.* 2003) and the presence of behavioural and psychological symptoms of dementia (BPSDs; Tun, *et al.* 2007), particularly psychotic symptoms (Scarmeas, *et al.* 2005).

Therefore, the aim of this study was to examine the influence of cognitive status, ADLs and the presence of BPSDs at the time of diagnosis on the survival of patients with treated probable Alzheimer disease (AD) seen in a tertiary-referral clinic. The objectives were to identify any predictors of survival from the above-mentioned factors.

Methods

Sample

As described in detail by Starr (2007) and Starr and Lonie (2007a, 2007b, 2008), the sample comprises consecutive patients seen at a tertiary-referral memory treatment centre covering the Lothian region (Lothian Memory Treatment Centre; LMTC) between February 2000 and July 2001. Routine assessment data were collected as part of a service evaluation approved by the Director of Public Health. The patients were included if they were diagnosed with probable AD—diagnosis was consensus-based involving two old age psychiatrists, a geriatrician and a neuropsychologist using NINCDS-ADRDA criteria (McKhann, *et al.* 1984)—and commenced on a cholinesterase inhibitor (either donepezil or rivastigmine).

Measures

The patients attending the LMTC completed a battery of seven cognitive tests, shown in Box 1. ADLs were measured using the instrumental activities of daily living (IADL) and the physical self-maintenance scales (PSMS; both Lawton and Brody 1969). The patients and carers also completed the Neuropsychiatric Inventory (NPI; Cummings, *et al.* 1994).

Text Box 1. Cognitive battery in the present sample[a]

Cognitive test	*Reference*	*Comments*
National adult reading test *(NART-IQ)*	Nelson, 1982	The patient is asked to read aloud a list of 50 irregularly-pronounced words. McGurn *et al*. (2004) validated this test as an estimate of pre-morbid full-scale IQ in a subgroup of this cohort. Higher score = more able.
Mini-mental state examination *(MMSE)*	Folstein, *et al*.1975	Tests a broad range of cognitive domains and scored out of 30. Higher score = more able.
Hopkins verbal learning test *(Hopkins)*	Brandt 1991	The total score of the three trials of free recall were used from this test of recent verbal memory/new learning ability. Higher score = more able.
Category (semantic) fluency *(Animals)*	Lezak 2004	This common test of executive function also tests semantic memory. The patient is asked to name as many animals (or fruit or vegetables or any other category) as possible in a minute. Higher score = more able.
Lexical verbal fluency *(FAS)*	Lezak 2004	Similar to category fluency but with the extra demand of set-shifting. The patient is asked to name as many words as possible beginning with letter F (and then A and then S) in one minute. Higher score = more able.
Paired-associate learning *(PAL)*	Robbins, *et al*.1994	Subtest from the Cambridge Automated Neuropsychological Test Assessment Battery (CANTAB) of visual and working memory. Higher score = more able.
Delayed matching to sample *(DMTS)*	Robbins *et al*.1994	Subtest from the CANTAB visual and working memory battery. Higher score = more able.

[a]Previously described in Starr (2007) and Starr and Lonie (2007b).

Data linkage

Permission for data linkage was obtained from the National Health Service (NHS) Lothian Caldicott Guardian. The Information Services Division of NHS National Services Scotland linked the data with death certificate data from the General Register Office for Scotland, providing date of death and all causes mentioned on the death certificate for those who had died. The data supplied did not distinguish between immediate, underlying or contributory causes of death.

Prior to the merging of the anonymised dataset with the linked data, Scottish Index of Multiple

Deprivation (SIMD) ranks were obtained for each individual using their postcode (Scottish Government National Statistics 2009).

Calculation of survival times

Survival was calculated in months from an estimated assessment date using the patient's date of birth and age when assessed. The earliest and latest possible dates of assessment were calculated, giving longest and shortest possible survival times, respectively. A middle survival using the midpoint of the year or the patient's date of death, whichever was earlier, was also calculated.

Sensitivity analyses

In order to test the robustness of conclusions, a number of sensitivity analyses were carried out. The younger half of the cohort were assigned the shortest survival (i.e. worst prognosis) and compared with the older half who were assigned the longest survival. Similarly, *post-hoc*, the half with lower scores on PAL were compared with the half with higher scores and the half with lower scores on the NPI psychotic factor were compared with the half with higher scores. Furthermore, age by gender interaction was examined in all univariate models.

Confounding

A potential confounder of survival in dementia is antipsychotic medication use, data for which were not available for this cohort, because the patients with more BPSD (and therefore higher NPI scores) might be more likely to be prescribed antipsychotic medications that might affect their survival (Schneider, *et al.* 2005; Wang, *et al.* 2005). Therefore, the NPI scores for the cases who had cerebrovascular disease mentioned on any part of their death certificate ($n = 87$, 17.3%) were compared with those without.

Statistical analysis

Data were analysed with the statistical package Predictive Analytics SoftWare version 18.0 (SPSS Inc., Chicago, Illinois; SPSS Inc., 2010). All covariates, apart from gender and drugs administered, were continuously scored. Age-adjusted univariate hazard ratios for men and women were similar, so data were pooled and gender-adjusted. The combined sample size was sufficient to detect hazard ratios of 1.31 at 80% power or 1.37 at 90% power (both with alpha at 0.05). Median survival times were calculated using the Kaplan–Meier method (Kaplan and Meier 1958). Cox regression (Cox 1972) was performed using stepwise entry of independent variables at $p < 0.05$ with age and gender forced into all models. The predictive capacity of each variable was examined separately. Next, multivariate models with the following variables were examined because they capture similar domains: MMSE and NART-IQ; the standard bedside battery of MMSE and tests of frontal lobe function; PAL and DMTS; PSMS and IADL; NPI (patient) and NPI (carer). The three NPI factors were also examined in a multivariate model. Subsequently, the best predictive model was constructed. Study members with missing data were excluded from individual models but all models were re-run using only cases with no missing data and hazard ratios were compared with those using the complete dataset.

Results

The analysis included 653 patients (459 women), mean age 77.1 years (SD 7.6, range 48–94 years). All the patients were treated with either donepezil (429, 66%) or rivastigmine (224, 34%). By the date of record linkage on 8 June 2010, 502 patients (77%) had died and data from death certificates were available for all of these. Baseline characteristics of the sample are shown in Table 1. All cognitive tests correlated

Table 1 Baseline characteristics of the present sample

Test[a]	*N*	Median	IQR	Range
MMSE	621	20	8	0–30
NART-IQ	351	107	15	0–128
Hopkins	596	9	6	0–32
Animals	599	7	5	0–24
FAS	599	20	18	0–67
PAL	456	4	3	0–17
DMTS	443	11	4	0–19
IADL	546	16	10	0–30
PSMS	543	7	3	0–23
NPI (patient)	551	11	14	0–67
NPI (carer)	550	5	9	0–56
SIMD rank	613	4306	3944	51–6504

[a]*MMSE*, Mini-mental state examination; *NART-IQ*, Estimated IQ using the national adult reading test; *Hopkins*, Hopkins verbal learning test; *Animals*, Category (Semantic) Fluency—naming animals; *FAS*, Lexical verbal fluency using the letters F, A and S; *PAL*, Paired-associate learning from CANTAB; *DMTS*, Delayed match to sample from CANTAB; *IADL*, Instrumental activities of daily living scale; *PSMS*, Personal self-maintenance scale; *NPI*, Neuropsychiatric inventory; *SIMD*, Scottish index of multiple deprivation.

strongly with each other, as did IADL and PSMS scores. NPI scores for the patient and the carer correlated significantly with each other and with the three factors, but these factors did not correlate with each other.

Effect estimates did not vary with survival time used (longest, middle or shortest) and so the middle survival was used.

Median survival was 65 months [interquartile range (IQR) 69]. Women survived significantly longer than men (71 months, IQR not calculable, versus 52 months, IQR 63; Log Rank $p = 0.001$) as did those treated with donepezil rather than rivastigmine (71 months, IQR 74, versus 54 months, IQR 67; Log Rank $p = 0.021$).

There were significant differences in survival between decade age groups (Log Rank $p < 0.001$). Median survival was 91 months for those aged from 50–59 (IQR not calculable), 85 months for those aged from 60–69 (IQR not calculable), 66 months for those aged from 70–79 (IQR 65), 53 months for those aged from 80–89 (IQR 61) and 33 months for those aged 90 or over (IQR 55).

Results of Cox regression models for each variable are shown in Table 2. Poorer performance on all cognitive tests—apart from DMTS which showed a non-significant trend—was significantly associated with worse survival. Higher NPI scores for the patient and carer were associated with poorer survival. Of the NPI factors, only the psychotic factor was significantly associated with worse survival, but the hazard ratio for the mood factor was also elevated. Choice of cholinesterase inhibitor did not significantly affect survival, but greater deprivation was significantly associated with worse survival.

Table 3 shows the results of the multivariate Cox regression models. Age had a consistently significant effect on survival with a hazard ratio of 1.33–1.42 in all models per standard deviation increase. Gender was significantly associated with survival but became non-significant with an attenuated effect in the more-adjusted models.

Both MMSE and NART-IQ were significantly associated with survival but only MMSE remained significant when both were included in the model. Entering the standard bedside battery of the MMSE and tests of frontal function (Animals and FAS), as recommended by the Mental Welfare Commission for Scotland (2007) for the assessment of dementia, resulted in both MMSE and Animals being significant covariates—that is, higher cognitive function and, specifically, better frontal lobe function, were associated with better survival. PAL remained a significant predictor of survival in a model with PAL and DMTS entered into it. Entering the three significant cognitive tests (MMSE, Animals and PAL) or indeed all the cognitive tests conducted identified PAL as a consistently significant covariate, that is, a higher PAL score was associated with better survival.

Of the measures of ADLs, IADL was significantly associated with survival but became non-significant when the patient's NPI score was included in a model. The patient's NPI score was significantly associated with survival but the carer's NPI score was not. Deprivation, measured by SIMD, was a significant predictor of survival in a univariate model but not in any multivariate model. Examining individual NPI factors (mood, psychotic and frontal) identified the psychotic factor as the only significant covariate. In a fully-adjusted model, the PAL and NPI psychotic factor remained significant predictors of survival.

The sensitivity analyses did not affect the results. There was little evidence of age by gender interaction following formal testing. Re-running all models using

Table 2 Age- and gender-adjusted univariate hazard ratios for the relation between study participant characteristics and mortality

Model[a]	Deaths	*N*	HR[c]	95% CI	*P*
MMSE	471	621	1.32	1.21, 1.44	<0.001
NART-IQ	264	351	1.13	1.01, 1.28	0.038
Hopkins	449	596	1.31	1.19, 1.45	<0.001
Animals	454	599	1.30	1.18, 1.44	<0.001
FAS	454	599	1.26	1.14, 1.39	<0.001
PAL	339	456	1.34	1.19, 1.50	<0.001
DMTS	328	443	1.11	1.00, 1.23	0.062
IADL	422	546	1.17	1.06, 1.30	0.002
PSMS	421	543	1.17	1.06, 1.28	0.002
NPI (patient)	430	551	1.20	1.09, 1.32	<0.001
NPI (carer)	428	550	1.12	1.03, 1.23	0.013
NPI mood factor	225	358	1.07	0.93, 1.22	0.38
NPI psychotic factor	225	358	1.18	1.04, 1.34	0.010
NPI frontal factor	225	358	0.99	0.86, 1.13	0.84
Drug[b]	502	653	1.09	0.90, 1.32	0.39
SIMD rank	472	613	1.11	1.01, 1.21	0.028

[a]*MMSE*, Mini-mental state examination; *NART-IQ*, Estimated IQ using the national adult reading test; *Hopkins*, Hopkins verbal learning test; *Animals*, Category (Semantic) Fluency—naming animals; *FAS*, Lexical verbal fluency using the letters F, A and S; *PAL*, Paired-associate learning from CANTAB; *DMTS*, Delayed match to sample from CANTAB; *IADL*, Instrumental activities of daily living scale; *PSMS*, Personal self-maintenance scale; *NPI*, Neuropsychiatric inventory; *SIMD*, Scottish index of multiple deprivation.

[b]Categorical variable: whether patient received donepezil (reference) or rivastigmine.

[c]Hazard ratios, computed using Cox regression analysis, are for one standard deviation disadvantage, apart from drug given.

Table 3 Hazard ratios for the relation of study participant characteristics with mortality (analyses are stepwise conditional entry with age and gender forced into the models as established risk factors for survival in dementia)

Model[a]	Deaths	*N*	*p*	HR[b] (95% CI)	Variables included in the model but statistically non-significant ($p > 0.05$)
Age	502	653	<0.001	1.35 (1.23, 1.48)	–
Male gender			<0.001	1.44 (1.19, 1.73)	
Age	471	621	<0.001	1.37 (1.24, 1.51)	–
Male gender			<0.001	1.43 (1.18, 1.74)	
MMSE			<0.001	1.32 (1.21, 1.44)	
Age	264	351	<0.001	1.42 (1.24, 1.63)	–
Male gender			0.059	1.29 (0.99, 1.68)	
NART-IQ			0.038	1.13 (1.01, 1.28)	
Age	263	350	<0.001	1.38 (1.20, 1.58)	NART-IQ ($p = 0.39$)
Male gender			0.098	1.25 (0.96, 1.63)	
MMSE			<0.001	1.32 (1.17, 1.48)	
Age	453	598	<0.001	1.33 (1.21, 1.48)	–
Male gender			<0.001	1.42 (1.17, 1.74)	
MMSE			0.008	1.17 (1.04, 1.32)	
Animals			0.004	1.19 (1.06, 1.35)	
Age	453	598	<0.001	1.36 (1.23, 1.50)	–
Male gender			<0.001	1.46 (1.19, 1.78)	
MMSE			0.002	1.21 (1.07, 1.36)	
FAS			0.042	1.13 (1.00, 1.27)	
Age	450	592	<0.001	1.32 (1.20, 1.46)	FAS ($p = 0.30$)
Male gender			<0.001	1.45 (1.19, 1.77)	
MMSE			0.005	1.18 (1.05, 1.33)	
Animals			0.004	1.19 (1.06, 1.34)	
Age	308	419	<0.001	1.33 (1.18, 1.51)	DMTS ($p = 0.23$)
Male gender			0.024	1.32 (1.04, 1.69)	
PAL			<0.001	1.36 (1.20, 1.53)	
Age	335	451	<0.001	1.35 (1.20, 1.52)	MMSE ($p = 0.11$) Animals ($p = 0.055$)
Male gender			0.014	1.34 (1.06, 1.69)	
PAL			<0.001	1.34 (1.19, 1.50)	
Age	338	455	<0.001	1.33 (1.18, 1.49)	MMSE ($p = 0.056$)
Male gender			0.013	1.34 (1.06, 1.69)	
PAL			<0.001	1.34 (1.20, 1.51)	
Age	205	278	<0.001	1.39 (1.19, 1.62)	MMSE ($p = 0.12$), NART-IQ ($p = 0.69$), Animals ($p = 0.12$), FAS ($p = 0.18$), Hopkins ($p = 0.11$), DMTS ($p = 0.60$)
Male gender			0.28	1.18 (0.87, 1.60)	
PAL			<0.001	1.35 (1.17, 1.57)	
Age	421	543	<0.001	1.39 (1.25, 1.55)	PSMS ($p = 0.26$)
Male gender			<0.001	1.51 (1.23, 1.86)	
IADL			<0.001	1.18 (1.07, 1.30)	
Age	428	549	<0.001	1.42 (1.28, 1.58)	NPI (carer) ($p = 0.50$)
Male gender			0.001	1.42 (1.16, 1.74)	
NPI (patient)			<0.001	1.20 (1.09, 1.32)	
Age	472	613	<0.001	1.39 (1.26, 1.53)	–
Male gender			<0.001	1.43 (1.18, 1.74)	
SIMD			0.028	1.11 (1.01, 1.21)	

(*Continues*)

Table 3. (Continued)

Model[a]	Deaths	*N*	*p*	HR[b] (95% CI)	Variables included in the model but statistically non-significant ($p > 0.05$)
Age	270	353	<0.001	1.42 (1.23, 1.63)	IADL ($p = 0.83$) SIMD ($p = 0.66$)
Male gender			0.038	1.32 (1.02, 1.71)	
NPI (patient)			0.003	1.21 (1.07, 1.36)	
PAL			<0.001	1.35 (1.18, 1.54)	
Age	225	295	<0.001	1.37 (1.17, 1.61)	NPI mood factor ($p = 0.42$) NPI frontal factor ($p = 0.83$)
Male gender			0.16	1.23 (0.92, 1.63)	
NPI psychotic factor			0.010	1.18 (1.04, 1.34)	
Age	175	236	0.001	1.39 (1.15, 1.67)	Animals ($p = 0.14$) IADL ($p = 0.88$) NPI (patient) ($p = 0.25$)
Male gender			0.39	1.15 (0.83, 1.60)	
PAL			0.007	1.25 (1.06, 1.47)	
NPI psychotic factor			0.012	1.21 (1.04, 1.40)	

[a]*MMSE*, Mini-mental state examination; *NART-IQ*, Estimated IQ using the national adult reading test; *Hopkins*, Hopkins verbal learning test; *Animals*, Category (Semantic) Fluency—naming animals; *FAS*, Lexical verbal fluency using the letters F, A and S; *PAL*, Paired-associate learning from CANTAB; *DMTS*, Delayed match to sample from CANTAB; *IADL*, Instrumental activities of daily living scale; *PSMS*, Personal self-maintenance scale; *NPI*, Neuropsychiatric inventory; *SIMD*, Scottish index of multiple deprivation.
[b]Hazard ratios, computed using Cox regression analysis, are for one standard deviation disadvantage, apart from gender.

only cases with no missing data ($n = 236$) gave similar results, but the effect of gender was attenuated (age-adjusted HR male gender 1.17, 95% CI 0.84, 1.62, $p = 0.35$). Characteristics of individuals with missing data and the non-missing dataset are shown in Table 4.

Table 5 shows the causes of death recorded on the patient's death certificates classified into categories adapted from Thomas *et al.* (1997). There were no differences between men and women apart from the general categories of 'other disease' ($t = -2.0$, $df = 333.5$, $p = 0.05$) and 'senility' ($t = -3.1$, $df = 603.3$, $p = 0.002$) but the former is a heterogeneous category and there were very few instances of men dying with 'senility' recorded on their death certificate ($n = 4$, 2.5%). Therefore, cause of death data for men and women were analysed together. One hundred and fifty-nine patients (31.7% deceased individuals) had pneumonia recorded as a cause of death and 36 (7.2%) senility or a similar non-specific category.

Table 4 Comparison of the characteristics of patients with complete data and those with any missing data

Variable[a]	No missing data (N = 236)	Missing data (N = 417)	*p*
Age (mean, sd)	78.0 (6.6)	76.6 (8.1)	0.020
Female (%)	70.3	70.3	0.98
Donepezil use (%)	64.8	66.2	0.73
MMSE (mean, sd)	20.6 (4.7)	18.5 (6.3)	<0.001
NART-IQ (mean, sd)	107.0 (10.2)	99.7 (28.4)	0.009
Hopkins (mean, sd)	10.2 (5.0)	8.7 (4.7)	<0.001
Animals (mean, sd)	8.8 (4.4)	7.2 (4.1)	<0.001
FAS (mean, sd)	24.7 (13.7)	20.4 (12.4)	<0.001
PAL (mean, sd)	4.5 (1.8)	4.1 (1.8)	0.016
DMTS (mean, sd)	11.4 (2.6)	10.8 (3.5)	0.022
IADL (mean, sd)	14.8 (6.2)	16.6 (6.5)	0.001
PSMS (mean, sd)	7.4 (2.7)	8.3 (3.3)	0.001
NPI (patient) (mean, sd)	12.6 (11.6)	14.0 (11.3)	0.156
NPI (carer) (mean, sd)	6.1 (6.6)	7.4 (7.4)	0.032
NPI mood factor (mean, sd)	−0.2 (0.98)	0.11 (1.10)	0.38
NPI psychotic factor (mean, sd)	0.01 (1.02)	0.00 (0.97)	0.96
NPI frontal factor (mean, sd)	0.02 (1.07)	−0.05 (0.70)	0.65
SIMD Rank (mean, sd)	4074.1 (1964.2)	3980.5 (2007.2)	0.57

[a]*MMSE*, Mini-Mental State Examination; *NART-IQ*, Estimated IQ using the National Adult Reading Test; *Hopkins*, Hopkins Verbal Learning Test; *Animals*, Category (Semantic) Fluency—naming animals; *FAS*, Lexical Verbal Fluency using the letters F, A & S; *PAL*, Paired Associate Learning from CANTAB; *DMTS*, Delayed Match to Sample from CANTAB; *IADL*, Instrumental Activities of Daily Living scale; *PSMS*, Personal Self-maintenance scale; *NPI*, Neuropsychiatric Inventory; *SIMD*, Scottish Index of Multiple Deprivation.

Table 5 Causes of death recorded on death certificates in the present sample by gender

	Male ($n = 160$, 82.5%)			Female ($n = 342$, 74.5%)		
Cause	n[a]	%[b]	% Lothian deaths (2009)[c]	n[a]	%[b]	% Lothian deaths (2009)[c]
Dementia	116	72.5	–	243	71.1	–
Pneumonia	54	33.8	2.8	105	30.1	4.0
Cardiac disease	35	21.9	20.9	76	22.2	15.9
Cerebrovascular disease	31	19.4	7.4	73	21.3	11.0
Neoplasms	21	13.1	31.7	37	10.8	27.6
Other vascular disease	15	9.4	–	30	8.8	–
'Senility' or other general term	4	2.5	–	32	9.4	–
Falls	7	4.4	1.0	19	5.6	1.8
Diabetes	7	4.4	0.9	15	4.4	1.1
Hip fracture	4	2.5	–	18	5.3	–
Other disease	58	36.3	–	102	29.8	–

[a]Number of deceased individuals from present sample with each cause mentioned on their death certificate.
[b]Percentages of causes of death for all deceased individuals add up to more than 100 because multiple causes were recorded for each individual.
[c]Lothian data are for all 2009 deaths from General Register Office for Scotland (2009)—data only available for routinely reported categories.

One hundred and eleven patients (22.2%) had cardiac disease and 45 (9.0%) had other vascular disease recorded on their death certificates.

Rates of all recorded categories of causes of death are higher than the rates for all deaths in 2009 in Lothian apart from neoplasms (rates for dementia, 'other vascular disease' and 'senility' were not available from data from the General Register Office for Scotland 2009; similarly, it was not possible to calculate a meaningful category of 'other disease' from available data). Hospital discharge data (Scottish Morbidity Record; SMR 01) estimate the crude prevalence of coronary heart disease in those aged over 75 to be 16.1% in Lothian (22.3% M, 12.3% F; ISD Scotland 2011) suggesting a slightly higher rate of cardiovascular disease in the women in this cohort with probable AD than the general female population.

Comparing individuals who died with cerebrovascular disease mentioned on their death certificate ($n = 87$, 17.3%) to those without revealed no significant differences in mean overall NPI scores, factor scores or relevant individual items (agitation, aggression, hallucinations or delusions) for which antipsychotics might be prescribed. This suggests that antipsychotic-related mortality has not confounded the results.

Discussion

The main finding of this study was that, in addition to increasing age and male gender, a lower score on PAL and the presence of psychotic symptoms at baseline were associated with significantly worse survival. Survival was consistently approximately 33%–42% worse per standard deviation increase in age at baseline in all models. Women survived longer in this study, as has been often shown in dementia (e.g. Stern, *et al.* 1997; Doody, *et al.* 2005; Sinforiani, *et al.* 2010 but not Brookmeyer *et al.* 2002), but the effect of gender became non-significant in models including more variables. Gambassi *et al.* (1999) have suggested that their observed gender-differences in mortality might result from different levels of comorbidity, but few gender-differences in causes of death were observed.

Predictors of survival

In this highly selected, tertiary-referral clinic sample, median overall survival was 65 months (5.4 years) and median survival by age-group was: 50–59—91 months (7.6 years), 60–69—85 months (7.1 years), 70–79—66 months (5.5 years), 80–89—53 months (4.4 years) and over 89—33 months (2.8 years).

Overall survival in this sample was slightly longer than the 4.9 years reported by Doody *et al.* (2005)—despite the wide recruitment strategy used in that study—and much longer than the 3.1 years reported from the Canadian Study of Health and Aging (Wolfson, *et al.* 2001), even though they estimated survival from onset of symptoms. Tsai *et al.* (2007) found a mean survival of 4.5 years in their memory clinic sample in China, though their AD death rate was only 28.9% compared with 77% in the current sample.

Rait *et al.* (2010) reported a comparable median survival for 60–69 year olds of 6.7 years (versus 7.1 years in this study) despite using a primary care sample rather

than a tertiary-referral sample. However, excluding untreated patients from our analysis would be expected to bias the results towards prolonged survival. Furthermore, treatment itself is unlikely to be associated with poorer survival.

In the present study baseline cognitive function, measured by MMSE, categorical verbal fluency (Animals) and PAL, predicted survival in this clinic sample of people with AD. However, in a model containing all the cognitive tests, PAL was the only significant predictor of survival. Prospective (Tsai *et al*. 2007; Andersen *et al*. 2010; Hötte *et al*. 2010) and retrospective studies (Landi *et al*. 1999) have found that baseline cognitive function—either measured by MMSE or severity of dementia—was significantly associated with increased mortality. However, Reisberg *et al*. (1996) found that mortality was not related to baseline dementia severity.

National Adult Reading Test score has been shown by McGurn *et al*. (2004), using a sample from this treatment centre, to be a reliable measure of premorbid full scale IQ in patients with dementia and, therefore, serves as a putative index of cognitive reserve (Whalley, *et al*. 2004; Richards and Deary 2005; Stern 2006; Stern 2009). NART-IQ was significantly associated with survival in a model including age and gender—in this study, individuals with lower estimated premorbid IQ declined more rapidly after diagnosis in contrast to the cognitive reserve hypothesis (Stern *et al*. 1999; Scarmeas *et al*. 2006). However, NART-IQ did not remain significant when MMSE was included in the model.

Both IADL and the patient's NPI score predicted survival in this sample. However, IADL became non-significant when further variables were included, and the NPI psychotic factor was the only element that significantly predicted survival. Newcomer *et al*. (2003) found that requiring maximum help in ADLs was associated with worse survival; this effect increased with the numbers of activities requiring assistance. Agüero-Torres *et al*. (1998) found that those who functioned worse declined faster. Miller *et al*. (2011), in the CATIE-AD trial, found that preserved ADLs were protective for nursing home admission, though they did not report predictors of survival.

Tun *et al*. (2007) found that survival was significantly lower in AD patients with more BPSD. Sinforiani *et al*. (2010) also found that higher NPI score at baseline was associated with earlier loss of autonomy. Scarmeas *et al*. (2005) reported that delusions and hallucinations were associated with faster decline, both in cognition and function, and that hallucinations were associated with increased mortality.

Causes of death

Bronchopneumonia is commonly reported in people dying with dementia (Morgan and Clarke 1995), up to 70.9% in presenile AD (Thomas *et al*. 1997). Table 5 shows a lower rate of pneumonia at death suggesting that other age-related causes of death might be more important in a late-onset dementia sample compared with patients with early-onset disease.

High rates of cerebrovascular disease and diabetes at death confirm the importance of cardiovascular risk factors, particularly diabetes, in the natural history of AD (Knopman, *et al*. 2001; Solfrizzi, *et al*. 2004; Luchsinger, *et al*. 2005; Whitmer, *et al*. 2005). The high rate of falls suggests that impaired mobility may be an important factor in the later stages of the disease. Indeed, Buchner and Larson (1987) found a very high fracture rate (15%) in a sample of patients with AD.

Limitations

The assessment battery used in this clinic is likely to be more extensive than that used elsewhere in the UK, though the treatment protocol will have been similar. Lothian has less of an ethnic mix than average in the UK but it provides a stable population, with migration particularly low in this age group.

Because the data were collected for a service evaluation—and not for research purposes—they do present limitations, and the date of assessment had to be estimated from the patient's date of birth and their age when assessed, as described above. However, there were no differences in effect estimates when the longest or shortest possible survival times were used, so a midpoint date of assessment was used to calculate survival.

Sensitivity analyses examining the effects of assigning worse survival to younger individuals, those with higher PAL scores and fewer psychotic symptoms did not alter the results. Furthermore, there was no evidence of age by gender interaction.

Details of prescribed medication were not available, but increased mortality related to antipsychotic medication (Schneider *et al*. 2005; Wang *et al*. 2005), as mentioned above, does not seem to have confounded the results: individuals with higher NPI scores—for

whom these medications might be prescribed—did not have an excess of cerebrovascular disease.

Cardiovascular disease and other risk factors, such as smoking, obesity and individual socio-economic status (as opposed to the area-based measure used here) are extremely important in dementia survival. The absence of these variables is a limitation of this study but because the clinic served the whole region of Lothian, there is likely to have been a wide spread of these risk factors, as shown by the range of SIMD ranks, and so confounding can be assumed to be minimal.

Although the sample is specific for the patients with treated probable AD, it has, by definition, excluded the patients with other dementias and the patients with untreated AD. The implications for survival of using a treated sample have been discussed above. In addition, it should be mentioned that this study does not allow us to comment on severe dementia because few patients had a baseline MMSE of lower than 12 ($n = 54$, 12.9%), in line with trial data and guidelines at the time.

Recording of causes of death on death certificates is widely acknowledged to be less than completely accurate, particularly for dementia (Martyn and Pippard 1988; Morgan and Clarke 1995). This is confirmed in this study because only 359 (71.5% of deceased) patients had dementia entered onto their death certificate. It is likely that other diseases are also underreported, perhaps not to the same extent, but this is impossible to estimate.

The comparison data are based on all deaths—because these were the only data available—but 79.5% deaths in Scotland in 2009 were older than 65 years (General Register Office for Scotland 2009) and the majority of the outcomes are age-related diseases. Proportions of deaths of individuals aged over 65 years were similar for all areas covered by the Lothian Memory Treatment Centre.

Conclusion

In addition to the anticipated impact of age and gender, the presence of psychotic symptoms and poor performance on PAL at baseline are also indicators of poor prognosis.

These clinic-based data indicate that at diagnosis, clinicians should not be optimistic or pessimistic about prognosis according to most measures of current cognitive status, pre-morbid mental ability, or current functional abilities, or the presence of other BPSDs. Age is a useful predictor of survival, with those over 90 years surviving less than 3 years on average. Common causes of death in people with AD were cardiovascular disease (in women) and falls: these represent opportunities at diagnosis for prevention to improve survival.

Key point

- In addition, to age and being female, CANTAB PAL score and the presence of psychotic symptoms were significant predictors of survival in AD.

Conflict of interest

TCR's post is funded by Alzheimer Scotland and he is employed in the NHS by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). TCR and JMS are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland.

TCR, GDB and JMS are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged.

GDB is a Wellcome Trust Fellow.

These data were presented as a poster at the Alzheimer's Association International Conference in Paris in July 2011.

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Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2012;41:1012–1032
doi:10.1093/ije/dys103

AGEING

Geographical variation in dementia: systematic review with meta-analysis

Tom C Russ,[1,2,3]* G David Batty,[4] Gena F Hearnshaw,[5] Candida Fenton[6] and John M Starr[1,2,3,7]

[1]Scottish Dementia Clinical Research Network, NHS Scotland, UK, [2]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK, [3]Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK, [4]Department of Epidemiology and Public Health, University College London, UK, [5]NHS North Yorkshire and York, UK, [6]MRC Social and Public Health Sciences Unit, Glasgow, UK and [7]NHS Lothian, UK

*Corresponding author. Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. E-mail: tom.russ@nhs.net

Accepted 1 June 2012

Background Geographical variation in dementia prevalence and incidence may indicate important socio-environmental contributions to dementia aetiology. However, previous comparisons have been hampered by combining studies with different methodologies. This review systematically collates and synthesizes studies examining geographical variation in the prevalence and incidence of dementia based on comparisons of studies using identical methodologies.

Methods Papers were identified by a comprehensive electronic search of relevant databases, scrutinising the reference sections of identified publications, contacting experts in the field and re-examining papers already known to us. Identified articles were independently reviewed against inclusion/exclusion criteria and considered according to geographical scale. Rural/urban comparisons were meta-analysed.

Results Twelve thousand five hundred and eighty records were reviewed and 51 articles were included. Dementia prevalence and incidence varies at a number of scales from the national down to small areas, including some evidence of an effect of rural living [prevalence odds ratio (OR) = 1.11, 90% confidence interval (CI) 0.79–1.57; incidence OR = 1.20, 90% CI 0.84–1.71]. However, this association of rurality was stronger for Alzheimer disease, particularly when early life rural living was captured (prevalence OR = 2.22, 90% CI 1.19–4.16; incidence OR = 1.64, 90% CI 1.08–2.50).

Conclusions There is evidence of geographical variation in rates of dementia in affluent countries at a variety of geographical scales. Rural living is associated with an increased risk of Alzheimer disease, and there is a suggestion that early life rural living further increases this risk. However, the fact that few studies have been conducted in resource-poor countries limits conclusions.

Keywords Dementia, Alzheimer disease, epidemiology, geography, disease clustering

Introduction

Tobler's first law of geography states that the relationship between entities is stronger when they are close than when they are distant.[1] In epidemiology, this is equally true for disease occurrence: clustered areas of low or high incidence may implicate environmental exposures associated with the disease, and this may have important public health consequences. Leukaemia demonstrates geographical clustering that may be related to proximity to nuclear facilities.[2,3] Similarly, the worldwide variation in multiple sclerosis rates suggests a complex interplay of genetic and environmental factors, such as climate, diet, geomagnetism, toxins and infection.[4–6] Clustering in both space[7,8] and spacetime[9] in schizophrenia has been described. Although systematic reviews of geographical variation in dementia exist,[10–12] previous aggregations of the evidence have relied on the *ad hoc* comparison of dementia occurrence across studies focusing on contrasting geographical locations (e.g. different countries or urban and rural areas).

However, data from a single study in one geographical location cannot be directly compared with those of another single centre study from another location because methodological differences between the studies; for example, differing diagnostic criteria or the way they are operationalized, may produce artefactual differences in prevalence or incidence. Accordingly, we provide an update of this evidence together with meta-analysis examining geographical variation in the prevalence and incidence of dementia from within-study comparisons.

Method

Information sources

We adopted a four-pronged approach to identifying relevant studies. First, we conducted an electronic search of relevant databases. Secondly, we scrutinized the reference sections of identified publications. Thirdly, we contacted experts in the field. Fourthly, we re-examined papers already known to us. Searches were conducted by an information scientist (C.F.). Table 1 shows databases utilized with dates. Comprehensive search criteria were developed iteratively. The full electronic search strategies for all databases used, including limits applied, are reported in the Supplementary Appendix A1. Results of the literature search were independently screened in parallel by two reviewers (T.R. and G.H.). Abstracts of relevant titles were reviewed and the full text of each highlighted article was obtained.

Eligibility criteria

Inclusion criteria were as follows: cross-sectional and longitudinal studies of any length offering a comparison of dementia prevalence or incidence between two or more different sites, at any geographical scale. Grey literature and theses were included. We did not limit the search by language (as long as there was an English language abstract) with the intention of having relevant papers translated. We also included papers in languages other than English if other reports from the same study had been published in English to allow adequate assessment of the methodology, and this further report contained relevant data. Articles could consider all causes of dementia apart from those secondary to external causes or where dementia is a later secondary feature of the disorder, e.g. alcohol or traumatic brain injury, Parkinson's disease, Huntington's disease and Creutzfeld Jakob disease, either sporadic or variant.

Exclusion criteria were as follows: papers comparing studies using external comparison groups, which were conducted independently or which used different methodologies (for example, the European Community Concerted Action on the Epidemiology and Prevention of Dementia/European Collaboration on Dementia papers[13–16] or other 'quantitative integrations of the literature'[10]), studies with no spatial variable (e.g. comparing different ethnic groups or investigating aluminium or silicate concentrations in water) and references with no abstract and a vague title (e.g. 'epidemiology of dementia'). Studies focusing purely on young onset dementia were excluded to reduce heterogeneity in the review.

Table 1 Databases searched and dates of searches

Database	Database start	Date searched
ASSIA (Applied Social Science Index)	1987	8 April 2010
Embase	1974	8 April 2010
FRANCIS	1984	8–9 April 2010
GEOBASE	1980	8 April 2010
Global Health	1973	9 April 2010
LILACS	1982	9 April 2010
Medline	1950	8 April 2010
PsycINFO	1806	8 April 2010
CINAHL	1981	8 April 2010
COPAC	1100	14 April 2010
SciELO	1997	14 April 2010
EThOS (British Library Electronic Theses Online Service)	–	14 April 2010
Australian Digital Theses (ADT) Program	1998	14 April 2010
Index to Theses	–	14 April 2010
ProQuest Dissertations and Theses	1861	15 April 2010
Theses Canada Portal	1965	15 April 2010
Conference Papers Index	–	15 April 2010
PapersFirst	1993	15 April 2010
ProceedingsFirst	1993	15 April 2010

A large number of papers describe the clusters of amyotrophic lateral sclerosis/parkinsonism–dementia complex in the Pacific basin. This cluster was included because the condition is prominently characterized by dementia. Due to the wealth of literature describing these isolated clusters, a representative paper was selected for inclusion.

Data collection

The principal summary measure was the prevalence or incidence of dementia in the two (or more) areas studied. Other data collected were the scale of comparison or areas that were compared, methods (including diagnostic criteria) and measures used, details and number of participants, including ages. The studies were also assessed for quality of design and methodology from A (best) to E (worst), including a consideration of bias. This measure of quality took into account quality and limitations of case-finding procedures, diagnostic criteria used, standardization across sites and completeness of follow-up in longitudinal studies.

Estimates of error were not reported by all authors, limiting the precision of comparisons of reported prevalence or incidence rates. Where possible, reported *P*-values were converted to 95% confidence intervals (CIs).[17]

Meta-analysis

Numbers of cases and non-cases in the studies comparing prevalence or incidence of dementia in rural and urban areas were used to compute odds ratios (ORs) with accompanying 90% CIs, in line with statistical guidance.[18] Urban areas formed the referent in all models. Where raw numbers were not reported, ORs and 95% CIs were converted to log ORs and log variances. These study-specific estimates of prevalence and incidence were meta-analysed, using random-effects models because there was a large amount of heterogeneity (prevalence studies: $I^2 = 90.8\%$; incidence studies: $I^2 = 81.2\%$). Authors of studies reporting insufficient data[19–21] were contacted, apart from Leighton *et al*.[22] for whom contact details were unavailable.

Sensitivity analyses

One prevalence study classified participants according to more than one set of diagnostic criteria.[23] In the main analyses, the results using Diagnostic and Statistical Manual of Mental Disorders, fourth revision (DSM-IV) criteria were used. We also examined the effect of altering the diagnostic criteria used and the effect of excluding the study completely from the models. We conducted a further sensitivity analysis stratifying the prevalence and incidence meta-analyses by study quality.

Statistical analyses were conducted using R version 2.15.0[24] and the metafor package.[25] Figures 3 and 4 were drawn with the R package Rmeta.[26] The reporting of this systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[27]

Results

A total of 12 580 records were screened, and the two reviewers (T.R. and G.H.) produced shortlists of 164 and 173 papers, respectively, that potentially matched inclusion criteria. Of 163 papers examined, 112 studies were excluded (reasons for exclusion are outlined in Figure 3, which shows the screening process), leaving 51 articles (from 35 unique studies), which are summarized in Tables 2–6.

The studies included were conducted across the world, though predominantly in high-income countries (Europe, Canada and the USA). The studies ranged in size from 321[28] to the entire population of the USA.[29] Methodologies included multiple-phase population surveys ($n = 13$[19,21,30–50]), one-phase surveys ($n = 10$[22,23,28,51–59]), using death certificate data ($n = 8$[20,29,49,60–65,88]) and case registers ($n = 3$[66–72]). Eight studies included a longitudinal design allowing dementia incidence to be ascertained.[19,31,34–35,38–41,43,58,59]

Diagnostic criteria used included the International Classification of Diseases (ICD), 9th revision[73] ($n = 5$[20,53,59,63,68–70]) or ICD-10[74] ($n = 8$[29,35–37,38,42,43,46,47,50,60,62,65]), DSM-III[75] or DSM-III-R[76] ($n = 8$[30,32–36,39,42–45,48,49,52]) or DSM-IV[77] ($n = 5$[19,23,46,47,50,57,58]). Three studies did not state the diagnostic criteria they used.[22,61,64,88] Tests used included the Mini-Mental State Examination[78] (MMSE) in various languages ($n = 9$[19,21,30,31,37,38,40,41,46,47,49–51]), the modified MMSE[79,80] (3MS; the Canadian Study of Health & Aging[32–34,39]), the Community Screening Instrument for Dementia[81] (CSID; the Ibadan–Indianapolis study[35,36,42,43]), the cognitive part of the Cambridge Examination for Mental Disorders of the Elderly[82] (CAMCOG; $n = 2$[31,40,41,50]), the Comprehensive Assessment and Referral Evaluation (CARE) or short-CARE interview[83] ($n = 2$[28,54]) and the Mental Status Questionnaire[84] (MSQ) or Short Portable MSQ[85] ($n = 2$[28,59]). Three studies[31,40,41,52,55,56] used the Geriatric Mental Schedule (GMS) and the Automated Geriatric Examination for Computer Assisted Taxonomy[86,87] (AGECAT). Thirteen studies included a clinical assessment of participants.[19,21,30,32–39,42–49,50,58,66,67,71]

The papers included in the review were divided into groups reflecting the scale of comparison. Each group will be considered, in turn, comparing rates between countries or nationwide surveys, rural and urban areas, regions, towns or cities and smaller areas.

Country-by-country comparisons or nationwide surveys

Table 2 summarizes the results of the studies identified which compared rates of dementia between countries. There were two main methodologies used

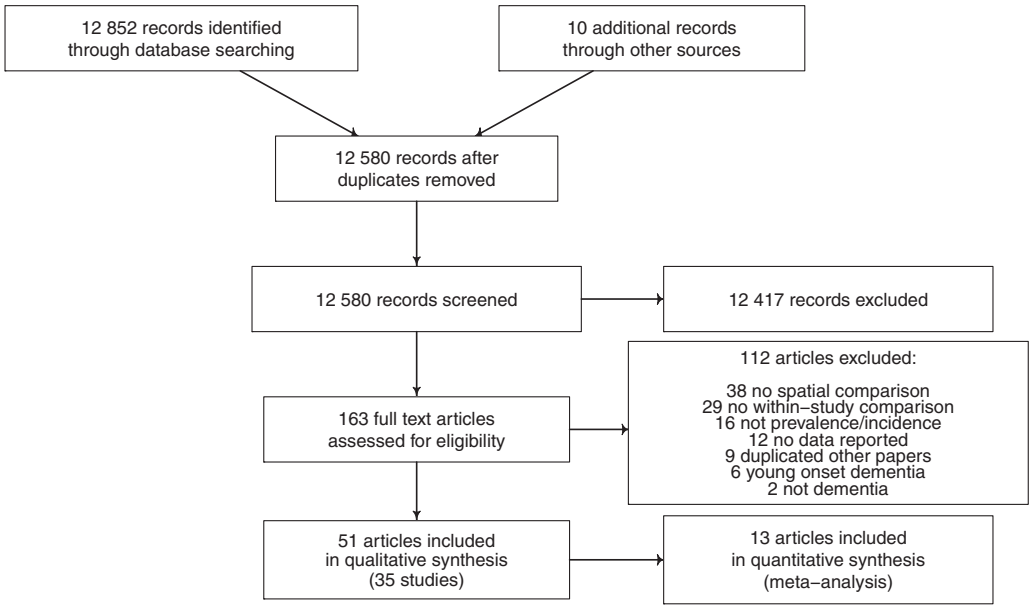

Figure 1 PRISMA diagram showing selection of studies for inclusion in systematic review of geographical clustering of dementia prevalence and incidence

at this scale: comparing mortality rates (of the whole population or a sample) between two or more countries and identifying the country of birth of individuals in a discrete area in a single country.

Age-adjusted Alzheimer disease (AD) mortality in 1999 was reported as 15.9% in the USA compared with 21.2% in Puerto Rico.[60] Rates for 2004 were 20.9 and 32.4%, respectively. They conjectured that the increase in dementia rates might be explained by improved survival.

The 'Colombo 2000' project found disease-specific mortality rates for AD to be higher in Italy (9.8/10 000) than in Argentina (3.4/10 000), which has a large Italian immigrant population.[64,88] Another study comparing random samples of the over 60s found that the proportion scoring less than 20 out of 30 on the MMSE was 4.5% in Argentina, 9.4% in Chile and 7.2% in Cuba.[51] With a higher cut-off of 22 or less out of 30, the proportions were 8.4% in Argentina, 19.7% in Chile and 16% in Cuba.

The 10/66 Dementia Research Group focuses particularly on the under-researched (and therefore resource-poor) areas of the world.[23,57] The authors found a much lower prevalence of dementia by DSM-IV than by 10/66 consensus criteria in India (rural and urban) and Peru (rural only) (Figure 2). Dementia prevalence was found to vary between countries, although the directly standardized prevalence rates differed with the diagnostic criteria used; compared with other sites, prevalence of dementia was higher in Cuba (10/66 criteria: 12.6%, 95% CI 10.4–14.9; DSM-IV: 6.3%, 95% CI 5.0–7.7) and the Dominican Republic (10/66 criteria: 9.8%, 95% CI 8.1–11.1; DSM-IV: 4.2%, 95% CI 3.3–5.1) and lower in rural China (10/66 criteria: 4.8%, 95% CI 3.1–6.4), rural Peru (DSM-IV: 0.4%, 95% CI 0.0–1.0) and both rural (DSM-IV: 0.3%, 95% CI 0.1–0.5) and urban (DSM-IV: 0.9%, 95% CI 0.3–1.6) India.

The remaining studies used the second methodology mentioned earlier—identifying the country of birth of individuals in a single area, thus providing insight into the effect of place of birth on the risk of developing dementia. The Islington study interviewed house to house and grouped the over 65s by country of birth.[54] They found no relation between migration *per se* and dementia. However, the relative risk (RR) for developing dementia did vary by place of birth, being lower in the Irish population (RR: 0.36, 95% CI 0.15–0.87) and higher in the case of people born in Africa or the Caribbean (RR: 1.72, 95% CI 1.06–2.81) when compared with British-born residents. Another London-based study found a higher dementia prevalence in African–Caribbean-born residents of Haringey compared with the White UK-born population (OR = 3.07, 95% CI 1.28–7.32).[50]

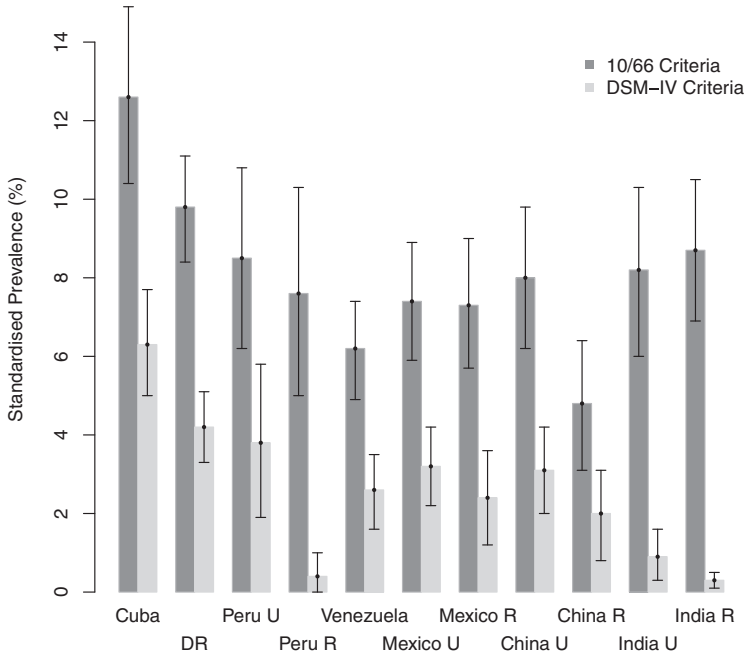

Figure 2 Comparison of standardized dementia prevalence (95% CI) with different diagnostic criteria. Constructed from 10/66 Dementia Research Group data.[23] DR = Dominican Republic, U = urban, R = rural

Study [reference]	Country	Rural+	Rural–	Urban+	Urban–	OR (90% CI)
Ogunniyi et al (2000) [42]	Nigeria					1.57 (0.44–5.56)
Ogunniyi et al (2000) [42]	USA					2.49 (1.21–5.12)
Lin et al (1998) [37]	Taiwan	70	1737	38	1070	1.13 (0.81–1.59)
Matthews et al (2005) [40]	UK	78	1296	139	2044	0.89 (0.70–1.13)
Zhang et al (2006) [47]	China					1.50 (1.29–1.75)
Rodriguez et al (2008) [23]	Peru	2	550	41	1338	0.12 (0.04–0.39)
Rodriguez et al (2008) [23]	Mexico	22	978	40	962	0.54 (0.35–0.84)
Rodriguez et al (2008) [23]	China	24	978	35	1125	0.79 (0.51–1.23)
Rodriguez et al (2008) [23]	India	8	991	9	977	0.88 (0.39–1.96)
Jean et al (1996) [67]	Canada	98	45724	121	85724	1.52 (1.21–1.90)
Yip et al (1997) [49]	Taiwan	9	396	20	1018	1.16 (0.59–2.25)
Arslantas et al (2009) [21]	Turkey	189	982	73	1856	4.89 (3.87–6.19)
Azzimondi et al (1998) [30]	Italy	80	267	116	264	0.68 (0.52–0.90)
Overall						**1.11 (0.79–1.57)**

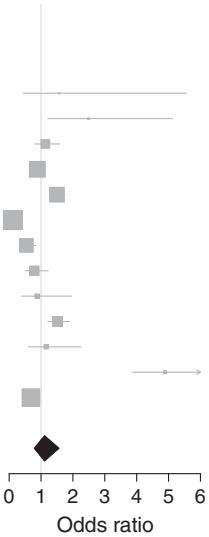

Figure 3 Meta-analysis with forest plot of urban/rural differences in dementia prevalence (using DSM-IV criteria for Ref. 23). Rural+: dementia cases in rural areas, Rural−: non-dementia cases in rural areas, Urban+: dementia cases in urban areas and Urban−: non-dementia cases in urban areas. Articles without case numbers reported ORs and 95% CIs rather than raw numbers. Urban areas form the referent

Table 2 Studies meeting inclusion criteria: country–country comparisons or surveys comparing country of birth

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Anzola-Perez *et al.*	1996	Pan American Health Organization (PAHO) study[51]	Argentina, Chile and Cuba	One-phase survey	Spanish MMSE	MMSE score	Age- and sex-stratified random community samples	⩾60	3211	Variable	D: methodologies differ slightly
Cristina *et al.* Román	1997, 1998	'COLOMBO 2000' project[64,88]	Argentina and Italy	Death certificate data	–	Not stated	All AD deaths	Not defined	90.8 million	Not stated	E: relies on diagnosis being recorded; population age-structures different
Livingston *et al.*	2001	Islington study[54]	Islington, London	One-phase survey	Short-CARE interview	Short-CARE	Random sample stratified by country of birth	⩾65	1085	107	C: good ascertainment; use of place of birth confounds migration and other factors
Figueroa *et al.*	2008	Ref. 60	USA and Puerto Rico	Death certificate data	–	ICD-10	All AD deaths	Not defined	Census	Not stated	E: relies on diagnosis being recorded
Rodriguez *et al.*, Sousa *et al.*	2008, 2009	10/66 Dementia Research Group[23,57]	Cuba, Dominican Republic, Mexico, Peru, Venezuela, China and India	Cross-sectional comprehensive one-phase surveys	–	10/66 criteria DSM-IV	All residents in geographically-defined catchment areas	⩾65	14 960	Not stated	B: screening difficulties possible; standardization between so many centres challenging
Adelman *et al.*	2011	Ref. 50	Haringey, London	Two-phase survey	MMSE CAMCOG	ICD-10 DSM-IV-TR Consensus criteria for sub-types	Random sample of General Practitioner (GP) lists stratified by recorded ethnic group	⩾60	436	36	C: robust design but spatial variable is confounded by migration

Table 3 Studies meeting inclusion criteria: rural/urban comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Leighton *et al.*	1963	Ref. 22	Nigeria: Yoruba villages and Abeokuta town	Population survey	–	Not stated	People with 'chronic brain syndrome'	Not defined	326	17 (estimated)	E: unclear
Imaizumi[a]	1992	Ref. 20	Japan	Death certificate data	–	ICD-9	All AD deaths	⩾35	Total population	931	E: relies on diagnosis being recorded
Emard *et al.*[a]	1992	Projet IMAGE[66,67,71]	Saguenay-Lac-Saint-Jean territory, Québec, Canada	Case register	Reisberg GDS	Adapted NINCDS-ADRDA	AD cases	Not defined	131 667 live births	235	C: dependent on quality of case register; case ascertainment and representativeness of sample unclear; differential mortality a potential bias
Perron *et al.*[a]	1993				Screening						
Jean *et al.*[a]	1996				Clinical assessment						
Ebly *et al.*[a]	1994	Canadian Study of Health and Aging[33,34,39]	All ten provinces of Canada	Two-phase screening	3MS	CSHA NINDS-AIREN DSM-III	Random sample from community and institutionalized residents	⩾65	5924	97	B: robust design but ascertainment unclear
Manfreda	1995			Incidence study (5 years)	Clinical assessment (including all institutionalised individuals)						
Hébert *et al.*[a]	2000										
Yip *et al.*	1997	Ref. 49	Taiwan: Ta-an district (urban) and Chin-shan Hsiang (rural)	Multiphase survey	Chinese MMSE	DSM-III-R	Random sample of community stratified by age	⩾65	1443	29	C: relatively robust but different response rates, 90% vs 71%
					ADL scales						
					Clinical assessment						
Liu *et al.*	1997	Refs. 38,37	Southern Taiwan	Two-phase screening Incidence study	Chinese MMSE	ICD-10-NA NINCDS-ADRDA	Random sample stratified by rurality	⩾65	2915	108	B: reasonable design
Lin *et al.*	1998				Blessed Dementia Rating Scale						
					Clinical assessment						
Azzimondi *et al.*	1998	Ref. 30	Sicily, Italy: Troina (isolated and rural) and S. Agata Militelo (a more developed small town)	Two-phase screening	Italian MMSE	DSM-III-R	50% random sample	⩾75	693	196	E: no power calculation and no statistical comparisons; clinical assessment only of sample of borderline cases, not all who screened negative
					Clinical assessment						
MRC CFAS[a]	1998	MRC CFAS[31,40,41]	UK: Four urban and two rural areas	Two-phase screening	GMS AGECAT	AGECAT	Stratified random community sample	⩾65	13 004 (prevalence)	214 prevalent 630 incident	B: Robust design; unreported measures; 2-fold variation in prevalence reasonable
Matthews *et al.*[a]	2005			Incidence study (2 years)	MMSE				7175 (incidence)		
Brayne *et al.*[a]	2006				GMS Assessment CAMCOG						
Hendrie *et al.*[a]	1995	Ibadan–Indianapolis study[36,42]	Ibadan, Nigerian and Indianapolis, USA	Two-phase screening	CSID	DSM-III-R and ICD-10	Community-dwelling Yoruba or sample of African Americans living in the community or in 6 representative nursing homes	⩾65	4706	93	A: robust identical methodologies
Ogunniyi *et al.*[a]	2000				Clinical assessment						

(continued)

Table 3 Continued

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Hendrie *et al.*[a]	2001	Ibadan1–Indianapolis study[35,43]	Ibadan, Nigeria and Indianapolis, USA	Incidence study (2 and 5 years)	CSID	DSM-III-R and ICD-10	Community-dwelling Yoruba or African Americans	⩾65	4606	187	A: robust identical methodologies
Ogunniyi *et al.*[a]	2006			Two-phase screening	Clinical assessment						
Zhang *et al.*[a]	2005	Refs. 46, 47	Four regions of China	Two-phase screening	Chinese MMSE	DSM-IV	Stratified, multistage, cluster random sample from census	⩾55	34 807	1027	B: thorough case-finding and 80–90% follow-up; crude prevalences reported
Zhang *et al.*[a]	2006				Clinical assessment	ICD-10					
					Re-examination at 6 months						
Bermejo-Pareja *et al.*[a]	2008	Neurologic disorders in central Spain[19]	Spain: Las Margaritas, greater Madrid (working class), Lista, central Madrid (professional class) and Arévalo (agricultural)	Two-phase screening	Spanish MMSE	Consensus	Census data for geographically defined areas	⩾65	5278 (prevalence)	306 prevalent	A: robust methodology
				Incidence study (3 years)	Pfeffer activities questionnaire	DSM-IV			3891 (incidence)	161 incident	
					Clinical assessment						
Rodriguez *et al.*[a]	2008	10/66 Dementia Research Group[23,57]	Cuba, Dominican Republic, Mexico, Peru, Venezuela, China and India	Cross-sectional comprehensive one-phase surveys	–	10/66 criteria	All residents in geographically defined catchment areas	⩾65	14 960	Not stated	B: sreening difficulties possible; standardization between so many centres challenging
Sousa *et al.*[a]	2009					DSM-IV					
Arslantas *et al.*	2009	Ref. 21	Eskisehir city, middle Anatolia, Turkey	Two-phase screening	Turkish MMSE	NINCDS-ADRDA NINDS-AIREN	Random cluster sample of geographically defined areas	⩾55	3100	262	D: relatively robust methodology but 49.5% who failed MMSE declined further assessment and no one with MMSE >25 was assessed further
					Clinical assessment						

[a]Articles also appear in another table.

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; ADL: Activities of daily living; GDS: Geriatric Depression Scale.

Table 4 Studies meeting inclusion criteria: regional comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Sulkava *et al.*	1985	Mini-Finland[44,45]	Finland	Two-phase screening	Cattel's G-factor test	DSM-III	Representative sample of Finnish population	⩾30 (⩾75 for dementia project)	8000	141	B: robust design and representative sample.
Sulkava *et al.*	1988				Verbal memory test						
					Clinical assessment						
Jorm *et al.*	1989	Ref. 63	Six Australian states	Death certificate data	–	ICD-9	All deaths 1979–85	Not defined	–	–	E: depends on dementia being reported
Zhang *et al.*	1990	Guam[72]	Guam, Mariana Islands, NW Pacific, 1956–85	Case register	Direct standardization of incidence rates using 1960 Chamorro population age distribution	Neuropathological and clinical criteria[90]	All cases of parkinsonism-dementia complex	Not defined	Not stated	340	C: completeness of case register may vary with time and location
Imaizumi	1992	Ref. 20	Japan	Death certificate data	–	ICD-9	All AD deaths	⩾35	Total population	931	E: relies on diagnosis being recorded
Canadian Study of Health and Aging Working Group	1994	Canadian Study of Health and Aging[32,33,39]	Five Canadian provinces	Two-phase screening	3MS	DSM-III	Random sample from community and institutionalized residents	⩾65	10 204 (1809)	1125 (515)	B: robust design but ascertainment unclear; Ebly *et al.* (1994) only included over-85s—in brackets[33]
Ebly *et al.*	1994				Clinical assessment (including all institutionalized individuals)						
Manfreda	1995										
Hébert *et al.*	2000	Canadian Study of Health and Aging[34]	All 10 Canadian provinces	Two-phase screening	3MS	CSHA NINDS-AIREN DSM-III	Random sample from community and institutionalized residents	⩾65	5924	97	B: robust design but ascertainment unclear
				Incidence study (5 years)	Clinical assessment (including all institutionalized individuals)						
White *et al.*	1994	Epidemiologic Studies of the Elderly[59]	USA: East Boston, Iowa and New Haven	One-phase survey	Short portable MSQ	SPMSQ ⩾3	Community population	⩾65	9174	1918	E: methods unclear, comparability questionable
				Incidence study (3 and 6 years)		ICD-9					
MRC CFAS	1998	MRC CFAS[31,40,41]	UK: Four urban and two rural areas	Two-phase screening	GMS AGECAT	AGECAT	Stratified random community sample	⩾65	13 004 (prevalence)	214 prevalent 630 incident	B: robust design; unreported measures; 2-fold variation in prevalence reasonable
Matthews *et al.*	2005			Incidence study (2 years)	MMSE				7175 (incidence)		
Brayne *et al.*	2006				GMS assessment						

(continued)

Table 4 Continued

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Hendrie *et al.*	1993	Ref. 48	Canada: Two Cree reserves in Northern Manitoba and Winnipeg	Two-phase screening	Initial interview Clinical assessment (culturally adapted)	DSM-III-R	All registered Cree Winnipeg: age-stratified sample from Health Insurance database	⩾65 (over-sampling of ⩾80s in Winnipeg)	468	31	C: comprehensive Cree register and reasonably comparable population, though institutional sample included; screening sensitive
Zhang *et al.*	2005	Ref. 46, 47	Four regions of China	Two-phase screening	Chinese MMSE Clinical assessment Re-examination at 6 months	DSM-IV ICD-10	Stratified, multi-stage, cluster random sample from census	⩾55	34 807	1027	B: thorough case-finding and 80–90% follow-up; crude prevalences reported
Zhang *et al.*	2006										
Laditka *et al.*	2008	Refs. 68–70	South Carolina, USA	Case register	–	ICD-9-CM	AD cases	Not defined	US census	33 754 (estimated)	B: very robust methodology but unclear when spatial analysis conducted (i.e. birth, adulthood etc.)
Laditka *et al.*	2006										
Laditka *et al.*	2006										
Figueroa *et al.*	2008	Ref. 60	USA and Puerto Rico	Death certificate data	–	ICD-10	All AD deaths	Not defined	Census	Not stated	E: relies on diagnosis being recorded
Bermejo-Pareja *et al.*	2008	Neurologic Disorders in Central Spain[19]	Spain: Las Margaritas, greater Madrid (working class), Lista, central Madrid (professional class) and Arévalo (agricultural)	Two-phase screening Incidence study (3 years)	Spanish MMSE Pfeffer activities questionnaire Clinical assessment	DSM-IV	Census data for geographically defined areas	⩾65	5728 (prevalence) 3891 (incidence)	306 prevalent 161 incident	A: robust methodology
Steenland *et al.*	2009	Ref. 29	USA 1999–2004	Death certificate data	–	ICD-10	All AD deaths	Not defined	1.7 billion	336 232	E: relies on diagnosis being recorded
Gillum *et al.*	2011	Ref. 65	USA	Death certificate data	–	ICD-10	All AD deaths 1999/2000 and 2005/06	Not defined	Not stated	555 904 dementia 211 386 AD (both 2005/06)	E: relies on diagnosis being recorded

Rural/urban comparisons

Table 3 outlines publications comparing rates of dementia in rural and urban areas. The rural/urban comparisons were quantitatively examined by meta-analysis where possible with the remaining studies being summarized narratively.

Papers that reported (or provided) sufficient prevalence[21,23,30,37,40,42,47,49,67] or incidence[19,34,40,43] data were meta-analysed using random-effects models, and results are shown in Figures 3 and 4, respectively. Urban areas form the reference group throughout. Out of the authors contacted, two replied providing data for inclusion in the meta-analysis.[19,21] Two articles were excluded due to reporting insufficient data.[20,22] The latest report from the 10/66 Dementia Research Group was excluded because it did not give sufficient data for inclusion despite reporting a slightly later stage of the study.[57]

There was evidence of an association between rurality and prevalence of AD[37,42,47,67] (OR = 1.50, 90% CI 1.33–1.69) but much less so for vascular dementia[30,37,47] (OR = 1.09, 90% CI 0.65–1.83). Evidence was weaker for an association between rurality and non-specific dementia prevalence[21,23,30,37,40,49] (OR = 0.91, 90% CI 0.57–1.45). Pooling all prevalence studies regardless of diagnostic subtype[21,23,30,37,40,42,47,49,67] resulted in an intermediate risk of dementia (OR = 1.11, 90% CI 0.79–1.57).

Only one prevalence study classified participants according to more than one set of diagnostic criteria.[23] Altering the criteria used had a substantial effect on the association between non-specific dementia and rurality: using DSM-IV criteria (OR = 0.91, 90% CI 0.57–1.45), using 10/66 consensus criteria (OR = 1.14, 90% CI 0.80–1.61) and excluding the four comparisons reported in this study (OR = 1.32, 90% CI 0.73–2.39). Combining all prevalence studies regardless of diagnostic subtype showed a similar pattern: DSM-IV (OR = 1.11, 90% CI 0.79–1.57); 10/66 criteria (OR = 1.26, 90% CI 0.97–1.65); and excluding the study (OR = 1.46, 90% CI 1.02–2.09).

Stratifying prevalence studies by quality reduced the association between rurality and dementia (studies rated D or better:[21,23,37,40,42,47,49,67] OR = 1.16, 90% CI 0.80–1.68, C or better:[23,37,40,42,47,49,67] OR = 1.03, 90% CI 0.80–1.32 and B or better:[23,37,40,42,47] OR = 0.95, 90% CI 0.69–1.29) apart from the two comparisons from the one study rated A for quality,[42] which captured early life rural living in which there was an increased association between rurality and AD (OR = 2.22, 90% CI 1.19–4.16).

There was evidence of an association between rurality and dementia incidence[19,34,40,43] (OR = 1.20, 90% CI 0.84–1.71), stronger for AD[43] (OR = 1.64, 90% CI 1.08–2.50) than for non-specific dementia[19,40] (OR = 0.81, 90% CI 0.61–1.09). Restricting the meta-analysis to incidence studies rated A for quality[19,43] (no incidence study was rated lower than B) had little effect on the association with rurality (OR = 1.17, 90% CI 0.66–2.06).

There was no evidence of publication bias on formal testing (regression test for funnel plot asymmetry: prevalence studies $z = -1.34$, $P = 0.18$; incidence studies $z = 1.51$, $P = 0.13$).[19,43]

Among the studies reporting insufficient data for meta-analysis, a study examining all Japanese death certificates from 1979 to 1990 found that the AD mortality was similar for rural and urban areas,[20] and a study in Nigeria found that prevalence of 'chronic brain syndrome' did not vary between Yoruba villages and a nearby town in men (6%) but did in women (5% vs 9%).[22]

Regional comparisons

'Region' here refers to an area within a country larger than a town or city. Table 4 summarizes the results of studies identified, which compared rates of dementia between regions.

The Canadian Study of Health & Aging reported a similar prevalence of dementia across Canada but suggested that the relative prevalence of dementia subtypes varied across regions.[32–34] Particularly low prevalence of dementia in Ontario men was explained by discrepancies in the use of diagnostic criteria.[32] Another Canadian study concluded that dementia prevalence varies little across regions.[39] They did note differences between community and institutional samples and noted that dementia prevalence was higher in areas of lower socio-economic status. In rural Manitoba, Canada, the prevalence of dementia among the Cree was found to be the same as a non-native sample in Winnipeg, but there was just one case of AD identified in the Cree (0.5%) compared with 20 in the Winnipeg sample (8.3%; age-adjusted rate: 3.5%, 95% CI 2.1–4.8; $P < 0.001$).[48]

A comparison of all dementia deaths in 1999/2000 and 2005/06 across the USA at the county level showed a pattern of marked variation in dementia and AD mortality different to that of cardiovascular disease and stroke.[65] Three 'co-operative longitudinal studies' in the USA reported 6-year incidence rates of 29.8% in East Boston, 25.0% in New Haven and 20.4% in Iowa.[59] Using stricter criteria reduced the variation between sites (East Boston 15.4%, New Haven 14.3% and Iowa 11.3%). Prevalence of AD in South Carolina showed 'notable variation' at a county level.[68–70] However, it was unclear whether the location was where the individual was born or where they were lived as an adult. Clustering of AD deaths in the north-west and south-east of the USA, with a 4-fold difference in rates between the highest and lowest was identified over the period of 1999–2004.[29] A study in Puerto Rico noted variation in mortality rates with dementia in the eight regions of the island.[60]

The amyotrophic lateral sclerosis/parkinsonism–dementia complex clusters in the Chamorro population of Guam (one of the Mariana Islands in the

Table 5 Studies meeting inclusion criteria: town/city comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Gurland *et al.*	1979	US–UK Geriatric Community Study[28]	New York and London	One-phase survey	MSQ CARE interview (modified)	MSQ ⩾8	Random sample of elderly in institutions	Not defined	321	117 (estimated)	C: reasonable methodology; small study
Ichinowatari *et al.*	1987	Ref. 53	Japan: Sashiki village and Ikema Island, Okinawa	One-phase survey One year of follow-up for confirmation	Not stated	ICD-9	Over 65s clinically diagnosed with dementia	⩾65	919	45	A: clinical assessment of entire populations
Copeland *et al.*	1987	US-UK Cross-National (Diagnostic) Project[52]	New York and London	One-phase survey	GMS AGECAT	AGECAT DSM-III (London only)	New York: random cluster sample London: random sample from 3000 GPs	⩾65	841	–	C: validity depends on AGECAT; DSM-III diagnosis confirms AGECAT diagnosis in London sample
Lobo Lobo *et al.*	1990 1992	Refs. 55, 56	Zaragoza, Spain and Liverpool, UK	One-phase survey	GMS AGECAT	AGECAT	Random age-stratified sample from census (Spain) or GP lists (UK)	⩾65	2150	134	D: unclear if comparison is an a priori hypothesis; random sampling subverted in Spain
Hendrie *et al.* Ogunniyi *et al.*	1995 2000	Ibadan–Indianapolis study[36,42]	Ibadan, Nigeria and Indianapolis, USA	Two-phase screening	CSID Clinical assessment	DSM-III-R and ICD-10	Community-dwelling Yoruba (total population survey of geographically-defined area) or African Americans living in the community (60% sample) or in six representative nursing homes	⩾65	4706	93	A: robust identical methodologies
Hendrie *et al.* Ogunniyi *et al.*	2001 2006	Ibadan–Indianapolis Study[35,43]	Ibadan, Nigeria and Indianapolis, USA	Incidence study (2 and 5 years) Two-phase screening	CSID Clinical assessment	DSM-III-R and ICD-10	Community-dwelling Yoruba or African Americans	⩾65	4606	187	A: robust identical methodologies
Artero *et al.*	2003	3C Study[58]	France: Bordeaux, Dijon and Montpellier	One-phase survey Incidence study (2 and 4 years)	Cognitive battery Clinical assessment (sample in Dijon)	DSM-IV	Random sample of non-institutionalized over 65s	⩾65	9294	637 (estimated)	C: reasonable methodology; in Dijon, screening estimated to be 87.5% sensitive and 78.8% specific

western Pacific Ocean) and elsewhere have been extensively studied.[89] A representative study on Guam identified an incidence gradient, with higher prevalence in southern and central Guam and lower prevalence in northern and western Guam.[72,90] More recent reports have not focused directly on the geographical spread of cases.[91] There have been suggestions that this cluster could be related to the consumption of a palm, *Cycas micronesica*, but this has not been definitively proven.[92] Similar clusters have been described on the Kii peninsula of Japan—with prevalence in two villages approximately one hundred times that in the rest of the country[93]—and in West New Guinea.[94]

Examination of Australian death certificates revealed a much higher prevalence of dementia at death in Tasmania and 'senility' in South Australia than the rest of the country.[63] Dementia prevalence at death was predominantly related to place of death, but those who were born and died in Tasmania had the highest rate of all. In Tasmania, 43% of dementia death certificates were linked to a single practitioner.

A Japanese study found that AD mortality varied across the country, with Miyazaki prefecture approximately double and Okinawa approximately half the overall national rate.[20] Across four areas of China, a north–south gradient in dementia prevalence, particularly for vascular dementia, and a less pronounced east–west gradient were identified.[46,47]

The Medical Research Council Cognitive Function and Ageing study concluded that there was no evidence of variation in incidence or prevalence of dementia in England and Wales.[31,40,41] The incidence of dementia in a working class urban area of Spain was double that in both the agricultural and professional class urban areas.[19] A Finnish study found a higher prevalence of AD in the north and east of the country than elsewhere.[44,45]

Town/city comparisons

Table 5 outlines the articles comparing rates of dementia between towns and cities.

The Ibadan–Indianapolis study identified a higher age-adjusted prevalence of dementia in Indianapolis, USA (4.82%) compared with Ibadan, Nigeria (2.29%; AD: 3.69% vs 1.41%).[36,42] At follow-up, age-standardized annual dementia incidence rates were higher in Indianapolis (3.24%, 95% CI 2.11–4.38; Ibadan: 1.35%, 95% CI 1.13–1.56), as were age-standardized annual AD incidence rates (Indianapolis: 2.52%, 95% CI 1.40–3.64; Ibadan: 1.15%, 95% CI 0.96–1.35).[35,43]

The rates of dementia in the institutionalized elderly population with moderate or severe dementia in New York and London were found to be similar.[28] A later study found that rates of organic illness were higher in New York for both men (5.7%; London 2.2%) and women (10.1%; London 5.4%).[52]

In Okinawa, there was some evidence of variation in rates of dementia between Sashiki village and Ikema island, but these were not formally compared and used as an idiosyncratic case classification.[53]

No difference in dementia prevalence was found between Zaragoza, Spain and Liverpool.[55,56] Furthermore, they identified no sex or age differences. The 3C study found no differences in the distribution of cognitive test scores in three cities across France.[58]

Small area comparisons

Large-scale (or small area) comparisons are potentially the most informative with regard to identifying socio-environmental risk factors for dementia. Table 6 outlines the papers making such comparisons.

Death certificates for the over 70s were examined in Newfoundland, Canada and two areas had substantially higher dementia mortality rates.[61] An excess of individuals born on the north shore of Bonavista Bay dying from dementia were identified (14.3%; south shore: 2.9%). This was not related to differential survival or sex distribution but may have been affected by kinship and migration. Projet IMAGE found no real variation in standardized prevalence rates of dementia in an area of Québec, Canada, despite a trend in two areas.[66,67,71] A Swiss study identified a dose–response relationship between the length of time living within 50 m of a power line and developing AD.[62]

Discussion

Main findings

All published studies indicate that the prevalence and, in one case, incidence of dementia varied between countries, but the precision of estimates was not always clear. Comparing rural and urban areas, there was evidence for an association between rurality and prevalence and incidence of AD. The association with AD prevalence was increased in studies that captured early life rural living. There was less evidence for an association with prevalence or incidence of a general category of dementia. At a regional level, the findings were mixed with some,[31–34,40,41] but not all,[19] of the better quality studies suggesting that there is little evidence of variation in dementia prevalence or incidence. However, very few studies report data supporting their findings, limiting the certainty of conclusions.

There were fewer large-scale studies and therefore conclusions must be tentative. However, the best quality studies did find variation in dementia incidence between towns/cities.[35,36,42,43] The 3C study[58] did not but reported the distribution of cognitive test scores rather than actual diagnoses of dementia. At the most informative (i.e. largest) scale, there were fewest studies. However, all except for Projet IMAGE[66,67,71] found evidence of variation in dementia prevalence. There were no studies of dementia incidence at this scale.

Table 6 Studies meeting inclusion criteria: small area comparisons

Author	Year	Study	Setting	Methods	Measures	Diagnostic criteria	Participants	Ages (years)	Total number	Cases	Quality (A–E)
Frecker	1991	Ref. 61	Newfoundland, Canada	Death certificate – data and case note scrutiny		Not stated	All deaths mentioning dementia 1985–1986	Not defined	7238	399	C: relies on diagnosis being recorded or sufficient information in case notes; very robust otherwise including controls for sex and survival biases
Emard *et al.*	1992	Projet IMAGE[66,67,71]	Saguenay-Lac-Saint-Jean territory, Québec, Canada	Case register	Reisberg GDS	Adapted NINCDS-ADRDA	AD cases	Not defined	131 667 live births	235	C: dependent on quality of case register; case ascertainment and representativeness of sample unclear; differential mortality a potential bias
Perron *et al.*	1993				Screening						
Jean *et al.*	1996				Clinical assessment						
Huss *et al.*	2009	Ref. 62	Switzerland	Death certificate – data linked to census		ICD-10	Community dwellers	⩾30	4.65 million	37 516	D: relies on diagnosis being recorded

To summarize, there is evidence, at all scales, of geographical variation in the prevalence or incidence of dementia and, specifically, a higher risk of AD in rural areas. At first glance, the different patterns seen at different scales seem contradictory and confusing. However, this is a common finding with geographical data, the *modifiable areal unit problem* where, 'if the spatial units in a particular study were specified differently, we might observe very different patterns and relationships'.[95] Unfortunately, none of the included studies collected their data or conducted their analyses at more than one scale, which might shed some light on this ubiquitous problem of spatial data.

The definition of rurality

There was substantial heterogeneity in the studies comparing rural and urban areas. This is likely to be due, at least in part, to the notoriously difficult definition of 'rurality'. A Japanese study defined an administrative unit as 'rural' if the population numbered 30 000 or fewer.[20] In Sicily, the isolation of rural Troina (where the 'economy is almost completely based on farming and grazing') is contrasted with the urban area 'connected by rail, sea, a regional road, and a motorway ... [where] the economy is more diversified'.[30] The 10/66 Dementia Research Group defined rural areas 'by low population density, and traditional agrarian lifestyle'.[96] Projet IMAGE defined a rural area as containing villages rather than cities.[97,98] Nevertheless, it is surprising how many studies do not explicitly define rurality—e.g. neither Liu *et al.*[38] nor investigators in the Canadian Study of Health and Aging[32,34,99] provided a definition of rurality. This is easier to understand when comparing extremes, for example a large city and distant villages, when the difference is obvious. However, it becomes more difficult to make subtle distinctions. Indeed, a perfect definition may remain elusive, and the epidemiological importance may not lie in the contrast but, rather, in the optimum population density (as has been demonstrated for cardiovascular disease and stroke in men[100]) and access to health services and factors conducive to a healthy lifestyle.

Young onset dementia

Although studies purely examining young onset dementia were excluded from this review, there are a number of relevant studies that echo the findings in late onset dementia. A study in Israel—using country of birth as the spatial variable—found age- and sex-adjusted incidence rates for European–American-born individuals to be double that of African–Asian-born people.[101] At a larger scale, a study in Edinburgh identified all 55 unrelated cases of young onset AD admitted to hospital and noted high prevalence in two geographical areas.[102] A subsequent study of young onset dementia across the whole of Scotland looked at the geographical

distribution of cases and found non-random distribution of cases of young onset AD but not vascular dementia.[103–106] This pattern was partly, but not entirely, explained by kinship, suggesting that socio-environmental factors may also play a role in the aetiology of young onset dementia.[104]

Limitations of the review and risk of bias within and across studies

The methodology of this review was systematic and robust and the wide, professionally conducted search, and two independent reviewers are likely to have identified all the available literature.

There is the possibility that variation in dementia prevalence or incidence might be the result of chance, but this review includes a large number of studies, many of them methodologically robust, which have found variation, suggesting that chance is unlikely to be behind all of them. Furthermore, all the studies included in the review offer within-study comparisons minimizing the possibility that identified variations in prevalence or incidence are the result of methodological differences between studies.

The first and most profound limitation to and source of bias in this review is the lack of attention paid to epidemiological studies of dementia in large areas of the world,[107] a point noted and beginning to be remedied by bodies such as the 10/66 Dementia Research Group,[23,57] also recently highlighted in relation to studies in Eastern and Middle European countries.[16] This is particularly important because it is predicted that increases in dementia prevalence will be larger in the developing world than elsewhere.[107,108] Until there are good quality epidemiological studies across the world, no conclusions regarding the global variation of dementia can be any less than conjectural.

There are significant methodological difficulties involved when comparing epidemiological studies, such as the method and thoroughness of case finding,[10] whether the entire population or a sample will be studied[109] and the choice of study setting itself. These difficulties are compounded in studies of dementia by consideration of different diagnostic criteria and whether to include mild cases,[10] let alone individuals with 'mild cognitive impairment'. Further biases, such as differential survival and consequent differing age structures of populations, variation in diagnosis rates and reporting of dementia,[63,110] screening non-participation and validation,[111] access to health care and levels of health and education make conducting and interpreting such studies—even when they are methodologically identical—extremely difficult.[11] These challenges are likely to have produced some bias in the studies and are reflected in the variation in quality ratings for the studies. One interesting finding from two studies[51,59] is that geographical variation reduces with stricter diagnostic criteria, confirming Jorm's assertion that the inclusion or exclusion of milder cases can have an important effect on the findings of quantitative studies of dementia.[10]

Considering diagnostic criteria in more detail, no studies investigated definitive neuropathological diagnoses, and therefore, differential rates of dementia subtypes must be considered no more certain than 'probable', in line with diagnostic criteria.[112–116] Therefore, the possibility remains that the clinical diagnoses reported in these studies may not perfectly reflect neuropathology, as has been shown previously.[117,118] The common neuropathological finding of mixed pathologies further complicates matters. This suggests that conclusions regarding specific dementia subtypes should be considered tentative.

A large number of studies rely on case registers or death certificate data. These methodologies are highly susceptible to bias in that the diagnosis has to be correctly made, recorded and transcribed into the appropriate record. Estimated rates of accurate dementia reporting on death certificates are 25–58%,[110,119] but more recent studies suggest that this is improving, for example, in a cohort of 502 deceased individuals with probable AD, 359 (71.5%) had dementia correctly recorded as a cause of death.[120] Furthermore, there is a potential spatial confounder in that clinical service provision or quality may vary with geography, resulting in variation of dementia prevalence as in one study where 43% of the cases in a cluster could be linked back to just one clinician, who presumably had a particular interest in dementia.[63]

Screening studies are more robust, particularly two-stage screening designs and especially when the whole population is screened rather than a sample. However, there is still a danger of selection bias creeping in.[111] The best quality studies included were the Neurologic Disorders in Central Spain Study[19] and, despite numerous methodological challenges—including estimating the ages of some of the Yoruba interviewed—the Ibadan–Indianapolis study.[35,36,42,43] Both studies showed variation in dementia incidence and the latter showed variation in AD prevalence.

The cultural validity of the tests and the rating scales, even if translated, is often unclear. Furthermore, cultural factors related to ageing and functional decline are also highly relevant to variation and a source of bias. Different cultures react to and accommodate ageing in different ways and will treat symptoms of cognitive and functional decline differently. We must not ignore the implicit value-laden nature of many, if not all, diagnoses,[121] even dementia—for example, what level of functioning can be expected at what age—and the variation of these values in different countries and different cultures. In fact, from a global perspective, the individual with dementia may not be a fixed kind of person but what Hacking describes as a 'moving target'.[122]

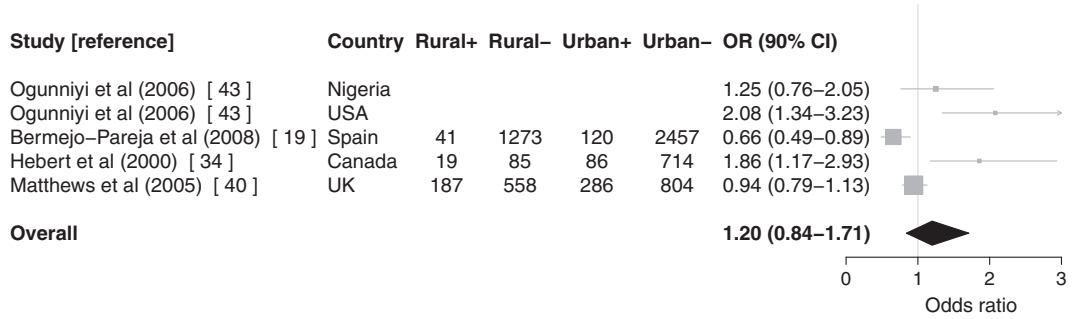

Figure 4 Meta-analysis with forest plot of urban/rural differences in dementia incidence. Rural^{+}: dementia cases in rural areas, Rural^{-}: non-dementia cases in rural areas, Urban^{+}: dementia cases in urban areas and Urban^{-}: non-dementia cases in urban areas. Articles without case numbers reported ORs and 95% CIs rather than raw numbers. Urban areas form the referent

Further potential confounders include differential survival or migration—for example, if individuals at a higher risk of developing dementia in an area die or move away, those remaining will have an artefactually low prevalence of dementia. Both migration[61] and differential survival[35,36,42,43,61] were considered by a small number of the studies. The methodology most susceptible to bias by migration is comparing country of birth of individuals living in a discrete geographical area. The finding that risk of dementia is increased in people born in Africa or the Caribbean[50,54] is not matched by increased rates of dementia in these countries that suggests migration may have confounded the studies using this methodology. Similarly, genetic relatedness is a factor that must be taken into account and was estimated by some of the studies included.[61,103,104,123]

The spatial variable must also be recorded from a sufficiently early point in life to avoid reverse causality, for example mapping the location of death of people with dementia may merely identify the locations of care homes or hospitals with long-stay beds.[110]

The relative dearth of larger scale comparisons—for example regions, towns or postal districts—limits the precise assessment of any variation that might be found and thus the conclusions that can be drawn about possible socio-environmental exposures.

This review explicitly excluded papers comparing studies conducted independently or with different methodologies. Therefore, there are potentially further studies looking at rates of dementia in rural areas, but the methodological difficulties in combining these with separate studies preclude such a comparison. This criterion is unlikely to have introduced substantial bias but clearly reduces the data available substantially with a consequent impact on CIs for effect estimates.

Implications

Apart from implications for health service provision, the real interest in identifying variation in the prevalence and incidence of a disease is in identifying potentially modifiable risk factors. Many socio-environmental risk factors are likely to have their effect on dementia risk early in life,[124–126] though not all studies confirm this association.[127] Some of the studies included in the current review examined early life effects, for example place of birth[61] or living in a rural area in childhood,[42,43] but the majority measured their exposures at the time of the study. The rural/urban meta-analysis suggested that, although rural living may be associated with increased rates of AD, early life rural living may have an even greater effect. There are two possible implications of this finding: that exposure in early life has a greater effect or that duration of exposure determines the risk. Further research is required to clarify this finding.

However, any consideration of geographical variation of dementia must also include geographical variation of related conditions and risk factors. Cardiovascular and cerebrovascular diseases have been shown to vary in incidence across Scotland, and this variation is partly related to smoking (in both sexes), population density, deprivation, blood pressure and body mass index (in men).[100] Temporal trends are also important. The possibility that changes in dementia incidence over time, and some geographical variation, might be related to improved survival following stroke has been raised.[128,129] Detailed examination of secular trends in dementia, related conditions and risk factors is required.[130]

Given the early effects of some risk factors and the presence of pathological changes of AD decades before the clinical onset of dementia,[131] any attempts at prevention will need to begin sufficiently early in life.

A number of systematic reviews have shown that modifying risk factors in late life, for example lowering blood pressure[132] or treatment with statins,[133] are ineffective in preventing dementia, consistent with the evidence that many risk factors for dementia have their effects in mid-life or earlier.[134–137]

This need for sufficiently early intervention is reflected in the ideal methodology of dementia epidemiology studies and the importance of measuring risk factors—including location—at the most appropriate time point. Identification of any putative risk factors, at any geographical scale, requires their measurement to be at a sufficiently early stage for the findings to be clinically meaningful.

Conclusions

Though the extant evidence is far from consistent and varies in quality, prevalence and incidence of dementia do vary, at a number of scales and between countries, regions, towns and cities and small areas. There is weak evidence for variation in dementia incidence or prevalence between rural and urban areas but stronger evidence for AD. Furthermore, early exposure to rural living may have an increased effect on the association between rurality and AD.

Further work to provide higher quality evidence of geographical and temporal variation is required, and comparisons could usefully be made with the geographical distributions of related conditions, such as stroke and cardiovascular disease. The next question is whether the causes of this observed variation can be identified, and, if so, could they highlight modifiable socio-environmental risk factors, thus making dementia a preventable disease?

Supplementary Data

Supplementary Data are available at *IJE* online.

Funding

T.C.R. is supported by Alzheimer Scotland and employed in the UK National Health Service (NHS) by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). T.C.R. and J.M.S. are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. T.C.R., J.M.S. and G.D.B. are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council and Medical Research Council (MRC) is gratefully acknowledged. G.D.B. is a Wellcome Trust Fellow. During the preparation of this manuscript, G.H. was employed by NHS Fife and, latterly, NHS Lothian. C.F. is employed by the MRC Social and Public Health Sciences Unit.

Acknowledgements

The authors would like to thank Dr Benito-León and Professor Özbabalık for providing additional data for the meta-analysis.

Conflict of interest: None declared.

KEY MESSAGES

- Identifying geographical variation in dementia prevalence and incidence could lead to the identification of potentially modifiable risk—or protective—factors.
- This review identifies evidence, based on within-study comparisons, at a variety of scales of geographical variation of dementia.
- Furthermore, there is evidence from meta-analysis of an association between rural living and AD, particularly for early life rural living.

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APPENDIX: Search Terms

Medline search

(Geograph* or cluster* or Afghanistan or Albania or Algeria or Angola or Antarctica or Argentina or Armenia or Australia or Austria or Azerbaijan or Bahamas or Bahrain or Bangladesh or Barbados or Belarus or Belgium or Belize or Benin or Bermuda or Bolivia or Bosnia or Botswana or Brazil or Brunei or Bulgaria or Burkina fasso or Burma or Burundi or Cambodia or Cameroon or Canada or Central African republic or Chad or Chile or China or Colombia or Congo or Costa Rica or Cote divoire or Croatia or Cuba or Cyprus or Czech republic or Denmark or Dominica or Dominican republic or Ecuador or Egypt or El Salvador or England or Equatorial guinea or Eritrea or Estonia or Ethiopia or Finland or France or Georgia or Germany or Ghana or Greece or Greenland or Guinea or Hong kong or Hungary or Iceland or India or Indonesia or Iran or Iraq or Ireland or Israel or Italy or Jamaica or Japan or Jordan or Kazakhstan or Kenya or Korea or Kuwait or Kyrgyzstan or Laos or Latvia or Lebanon or Lesotho or Libya or Lithuania or Malawi or Malaysia or Mali or Mexico or Mongolia or Morocco or Mozambique or Namibia or Nepal or Netherlands or New Zealand or Nicaragua or Niger or Nigeria or Norway or Pakistan or Papua new Guinea or Paraguay or Peru or Philippines or Poland or Portugal or Puerto Rico or Romania or Russia or Rwanda or Saudi Arabia or Scotland or Senegal or Serbia or Sierra Leone or Singapore or Slovakia or Slovenia or Somalia or South Africa or Spain or Sri lanka or Sudan or Swaziland or Sweden or Switzerland or Syria or Taiwan or Tajikistan or Tanzania or Thailand or Togo or Trinidad or Tunisia or Tunisia or Turkey or Turkmenistan or Uganda or Ukraine or United Arab Emirates or United kingdom or United states or Uruguay or Uzbekistan or Venezuela or Vietnam or Wales or Zambia or Zimbabwe).ab.

or

(Geograph* or cluster* or Afghanistan or Albania or Algeria or Angola or Antarctica or Argentina or Armenia or Australia or Austria or Azerbaijan or Bahamas or Bahrain or Bangladesh or Barbados or Belarus or Belgium or Belize or Benin or Bermuda or Bolivia or Bosnia or Botswana or Brazil or Brunei or Bulgaria or Burkina fasso or Burma or Burundi or Cambodia or Cameroon or Canada or Central African republic or Chad or Chile or China or Colombia or Congo or Costa Rica or Cote divoire or Croatia

or Cuba or Cyprus or Czech republic or Denmark or Dominica or Dominican republic or Ecuador or Egypt or El Salvador or England or Equatorial guinea or Eritrea or Estonia or Ethiopia or Finland or France or Georgia or Germany or Ghana or Greece or Greenland or Guinea or Hong kong or Hungary or Iceland or India or Indonesia or Iran or Iraq or Ireland or Israel or Italy or Jamaica or Japan or Jordan or Kazakhstan or Kenya or Korea or Kuwait or Kyrgyzstan or Laos or Latvia or Lebanon or Lesotho or Libya or Lithuania or Malawi or Malaysia or Mali or Mexico or Mongolia or Morocco or Mozambique or Namibia or Nepal or Netherlands or New Zealand or Nicaragua or Niger or Nigeria or Norway or Pakistan or Papua new Guinea or Paraguay or Peru or Philippines or Poland or Portugal or Puerto Rico or Romania or Russia or Rwanda or Saudi Arabia or Scotland or Senegal or Serbia or Sierra Leone or Singapore or Slovakia or Slovenia or Somalia or South Africa or Spain or Sri lanka or Sudan or Swaziland or Sweden or Switzerland or Syria or Taiwan or Tajikistan or Tanzania or Thailand or Togo or Trinidad or Tunisia or Tunisia or Turkey or Turkmenistan or Uganda or Ukraine or United Arab Emirates or United kingdom or United states or Uruguay or Uzbekistan or Venezuela or Vietnam or Wales or Zambia or Zimbabwe).ti.

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(Geograph* or cluster* or Afghanistan or Albania or Algeria or Angola or Antarctica or Argentina or Armenia or Australia or Austria or Azerbaijan or Bahamas or Bahrain or Bangladesh or Barbados or Belarus or Belgium or Belize or Benin or Bermuda or Bolivia or Bosnia or Botswana or Brazil or Brunei or Bulgaria or Burkina fasso or Burma or Burundi or Cambodia or Cameroon or Canada or Central African republic or Chad or Chile or China or Colombia or Congo or Costa Rica or Cote divoire or Croatia or Cuba or Cyprus or Czech republic or Denmark or Dominica or Dominican republic or Ecuador or Egypt or El Salvador or England or Equatorial guinea or Eritrea or Estonia or Ethiopia or Finland or France or Georgia or Germany or Ghana or Greece or Greenland or Guinea or Hong kong or Hungary or Iceland or India or Indonesia or Iran or Iraq or Ireland or Israel or Italy or Jamaica or Japan or Jordan or Kazakhstan or Kenya or Korea or Kuwait or Kyrgyzstan or Laos or Latvia or Lebanon or Lesotho or Libya or Lithuania or Malawi or Malaysia or Mali or Mexico or Mongolia or Morocco or Mozambique or Namibia or Nepal or Netherlands or New Zealand or Nicaragua or

Niger or Nigeria or Norway or Pakistan or Papua new Guinea or Paraguay or Peru or Philippines or Poland or Portugal or Puerto Rico or Romania or Russia or Rwanda or Saudi Arabia or Scotland or Senegal or Serbia or Sierra Leone or Singapore or Slovakia or Slovenia or Somalia or South Africa or Spain or Sri lanka or Sudan or Swaziland or Sweden or Switzerland or Syria or Taiwan or Tajikistan or Tanzania or Thailand or Togo or Trinidad or Tunisia or Tunisia or Turkey or Turkmenistan or Uganda or Ukraine or United Arab Emirates or United kingdom or United states or Uruguay or Uzbekistan or Venezuela or Vietnam or Wales or Zambia or Zimbabwe).sh.

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This search was then combined using 'AND' with

(Dementia or Alzheimer* or Alzheimer Disease or Aphasia, Primary Progressive or Primary Progressive Nonfluent Aphasia or Creutzfeldt-Jakob Syndrome or Dementia, Vascular or CADASIL or Dementia, Multi-Infarct or Diffuse Neurofibrillary Tangles with Calcification or Frontotemporal Lobar Degeneration or Frontotemporal Dementia or Primary Progressive Nonfluent Aphasia or Lewy Body Disease or Pick Disease of the Brain) af.

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(Prevalence or incidence or distribut* or epidem*).af.

limited to English Language and humans

This search strategy was used across all the larger bibliographic databases.

Simple search

For smaller databases a simpler search was used as follows

Prevalence or incidence or distribut* or epidem* or Geograph* or cluster*

and

Dementia or Alzheimer* or Alzheimer Disease or Aphasia, Primary Progressive or Primary Progressive Nonfluent Aphasia or Creutzfeldt-Jakob Syndrome or Dementia, Vascular or CADASIL or Dementia, Multi-Infarct or Diffuse Neurofibrillary Tangles with Calcification or Frontotemporal Lobar Degeneration or Frontotemporal Dementia or Primary Progressive Nonfluent Aphasia or Lewy Body Disease or Pick Disease of the Brain

This search was run across all fields.

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Does the Framingham cardiovascular disease risk score also have predictive utility for dementia death? An individual participant meta-analysis of 11,887 men and women

Tom C. Russ [a,b,c,*], Mark Hamer [d], Emmanuel Stamatakis [d], John M. Starr [a,b,c], G. David Batty [c,d], Mika Kivimäki [d]

[a] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK
[b] Scottish Dementia Clinical Research Network, NHS Scotland, UK
[c] Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK
[d] Department of Epidemiology and Public Health, University College, London, UK

ARTICLE INFO

Article history:
Received 20 December 2012
Received in revised form
30 January 2013
Accepted 11 February 2013
Available online 26 February 2013

Keywords:
Framingham study
Risk
Prediction
Mortality
Dementia
Cardiovascular disease
Meta-analysis

ABSTRACT

Objective: Individual cardiovascular disease (CVD) risk factors are associated with dementia. For the first time, we investigated whether the Framingham CVD risk score—which comprises these multiple risk factors—was also associated with future dementia risk.
Methods: Individual participant meta-analysis of two large, general population cohort studies ($N = 11,887$). For the purposes of comparison of the dementia results, we also examined the association between the Framingham CVD risk score and CVD-related death.
Results: Framingham CVD risk score was associated with dementia death (hazard ratio per 10% increased risk, 95% confidence interval: 4.00, 2.44–6.56). Adjusting for age eliminated this association (1.04, 0.53–2.01); similarly, age explained 88% of the ability of the Framingham CVD risk score to predict CVD death.
Conclusions: The Framingham CVD risk score was no more strongly associated with future dementia than age. It therefore offers no added value in predicting dementia.

1. Introduction

Cardiovascular disease (CVD) and dementia represent a major disease burden worldwide. These conditions share a series of risk factors (hypertension, smoking, obesity, diabetes, and dyslipidemia) [1]. CVD itself, particularly multiple strokes, also appears to elevate dementia risk [2]. The Framingham Cardiovascular Disease Risk Score [3], which comprises these risk factors, is a standard tool for assessing future risk of CVD in people who are apparently healthy. This raises the possibility that this risk score might also be useful in identifying people at increased risk of developing dementia. Since the Framingham CVD risk score is already commonly used in clinical practice, the implications of such an observation would be considerable.

While the Framingham CVD risk score has been shown to predict cognitive decline [4], an aspect of dementia, to the best of our knowledge, there are no prospective studies examining the links between the Framingham CVD risk score and future dementia [5]. Accordingly, we meta-analysed individual-participant data from two large English population-based cohort studies.

2. Methods

Participants were taken from the Health Survey for England [6], a series of annual, on-going, independent, general population-based cross-sectional studies that are representative of household-dwelling individuals in England in most years. Participants gave informed consent and ethical approval was obtained from the London Research Ethics Council.

The scientific focus of each survey changes year to year; risk factor data for calculating the Framingham CVD risk score [3] (age, sex, HDL-cholesterol, total cholesterol, systolic blood pressure, smoking, and diabetes) were available for surveys conducted in 1998 and 2003. Mortality follow-up of study members in these

* Corresponding author. Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. Tel.: +44 (0)131 650 4341; fax: +44 (0)131 242 6370.
E-mail address: tom.russ@nhs.net (T.C. Russ).

studies continued until death or 15th February 2008, whichever came first. Dementia- and CVD-related deaths [3] were identified from any mention on death certificates of the following codes: dementia—ICD-9 codes 290.0—290.4 (senile dementia, uncomplicated; presenile dementia; senile dementia with delusional or depressive features; senile dementia with delirium; or vascular dementia), 294.9 (unspecified persistent mental disorders due to conditions classified elsewhere), 331.0—331.2 (Alzheimer's disease; frontotemporal dementia; or senile degeneration of the brain), and 331.9 (cerebral degeneration, unspecified) and ICD-10 codes F01, F03, F09, G30, and G31; CVD—ICD-9 codes 410—414 (ischaemic heart disease), 428 (heart failure), 430—438 (cerebrovascular disease), 440 (atherosclerosis), and 443—445 (other peripheral vascular disease; arterial embolism and thrombosis; or atheroembolism) and ICD-10 codes I20-I25, I50, I60—I69, I70, I73, and I74 (characteristics of the two surveys are shown in Table 1).

Using similar methodology to previous studies [7], we used Cox proportional hazards models to compute study-specific effect estimates with accompanying standard errors which we pooled in a random effects meta-analysis. We report unadjusted hazard ratios (HR) with accompanying 95% confidence intervals (CI) per 10% increase (disadvantage) in the Framingham CVD risk score in relation to dementia-related deaths following the convention in testing multifactorial predictive algorithms [8]. Models were also adjusted for age and sex. We also ran models examining the association between the Framingham CVD risk score and CVD-related death to compare the predictive utility of the score for dementia with its original purpose.

In addition, we conducted a number of supplementary analyses: including only individuals aged <75 years since the Framingham CVD risk score is recommended for use in this age-group; using the Framingham CVD risk score having substituted BMI for HDL- and total cholesterol [3]; and dropping any dementia-related deaths during the first two years of follow-up in order to assess reverse causality. In a further sensitivity analysis, missing values for covariates were imputed with PASW statistics version 18.0 using five imputations. All other statistical analyses were conducted using R version 2.15.0.

3. Results

From an initial sample of 21,945 participants, 1997 did not consent to record linkage and 6071 had missing data. Additionally, we excluded 1990 with evidence of CVD at baseline. These exclusions resulted in an analytic sample of 11,887 (mean [SD] age 54.0 [13.2] years, range = 35—95). Individuals with missing data ($N = 6056$) were slightly older (55.2 [SD = 14.4] vs 54.0 [13.2], $p < 0.001$) and somewhat more likely to be female (58.9% female vs 54.4%, $p < 0.001$), the statistically significant differences arising from a large sample size rather than any sizeable absolute differences.

Table 1
Characteristics of the 1998 and 2003 Health Surveys for England.

	1998	2003	Total
N (complete data for all variables)	6656	5321	11887
Participants with missing data (%)	2721 (29.0)	3335 (38.9)	6056 (33.8)
Age			
mean [SD]	54.0 (13.4)	54.0 (12.9)	54.0 (13.2)
Range	35—95	35—94	35—95
Female (%)	53.9	55.1	54.4
Years of follow-up (mean [SD])	9.1 (1.6)	4.5 (0.5)	7.1 (2.6)
Number of deaths	713	162	875
Dementia deaths	50	4	54
Cardiovascular disease deaths	252	49	301
Ischaemic heart disease deaths	134	27	161
Cerebrovascular disease deaths	82	19	101

Of the 875 deaths during a mean (SD) follow up of 7.1 (2.6) years, 54 were dementia-related (13 Alzheimer disease, two vascular dementia, and 39 dementia sub-type not specified). Fig. 1 shows the relation of the Framingham CVD risk score with deaths from dementia and CVD. Higher Framingham CVD risk score was associated with increased risk of dementia death: each 10% increase (disadvantage) was associated with a 4.00-fold (95% CI 2.44—6.56) increase in the risk of dementia death ($p_{trend} < 0.001$). Adjusting for sex increased the magnitude of the association (HR 5.08; 3.50—7.37; $p_{trend} < 0.001$). Age is a part of the Framingham CVD risk score algorithm, but because dementia is age-related (HR per year increase: 1.21; 1.17—1.24) we additionally controlled for age in these analyses whereupon the association between the Framingham CVD risk score and dementia was eliminated (age-adjusted HR 1.04; 0.53—2.01; $p_{trend} = 0.91$).

Using CVD-related death as the outcome of interest also showed a substantial attenuation of the relationship after age-adjustment although, unlike dementia, there was still evidence of increased CVD risk. Thus, a higher Framingham CVD risk score was associated with 3.76-fold (95% CI 2.63—5.39; $p_{trend} < 0.001$) increased risk of CVD death per 10% increase in Framingham CVD risk score before, and 1.34-fold (0.73—2.45; $p_{trend} = 0.34$) risk after, age-adjustment.

None of the supplementary analyses, mentioned above, altered our conclusions. Restricting the models to individuals aged <75 years ($N = 10,828$; 12 dementia deaths, 128 CVD deaths) gave an unadjusted HR for dementia death of 3.96 (95% CI 0.92—16.99, $p_{trend} = 0.064$) and an age-adjusted HR of 0.96 (0.04—22.2, $p_{trend} = 0.98$). The unadjusted HR for the association between the Framingham CVD risk score-BMI and dementia death ($N = 14,148$; 53 dementia deaths) was 3.23 (95% CI 1.08—9.71; $p_{trend} < 0.001$). Dropping any deaths during the first two years of follow-up (49 dementia deaths) resulted in an unadjusted HR for dementia death of 2.34 (95% CI 0.46—11.84; $p_{trend} = 0.30$) and an age-adjusted HR of 0.37 (0.01—9.78; $p_{trend} = 0.55$).

Accounting for missing data by multiple imputation did not appreciably change the results: association between the Framingham CVD risk score and dementia death, unadjusted HR 3.63 (95% CI 2.78—4.73; $p_{trend} < 0.001$), age-adjusted HR 1.13 (0.83—1.53; $p_{trend} = 0.45$); association between the Framingham CVD risk score and CVD death, unadjusted HR 3.47 (2.93—4.11; $p_{trend} < 0.001$), age-adjusted HR 1.34 (1.05—1.71; $p_{trend} = 0.017$).

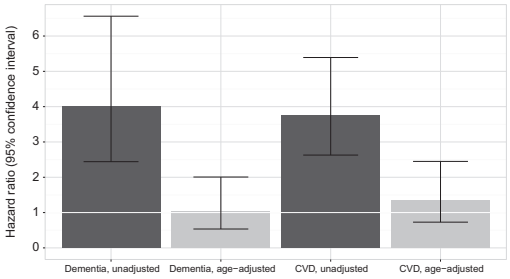

Fig. 1. Association of Framingham CVD risk score with dementia and CVD death over a mean 7.1-year follow-up. Hazard ratios (95% confidence intervals) are per 10% increase (disadvantage) in the Framingham CVD risk score in men and women who were free from dementia and CVD at baseline in the 1998 and 2003 Health Surveys for England ($N = 11,887$).

4. Discussion

The aim of the present analyses was to examine whether the Framingham CVD risk score was useful in predicting future risk of dementia. In a large population sample of adults who were free from CVD at study induction, we found an association between elevated Framingham CVD risk score and an increased risk of dementia death that was greater in magnitude than the relationship between Framingham CVD risk score and CVD-related death. However, the Framingham CVD risk score–dementia relation was lost when age was added to the multivariable model. While age also explained 88% of the ability of the Framingham CVD risk score to predict CVD it did not completely remove the association.

As described, there is evidence of an association between the Framingham CVD risk score and cognitive decline [4]. To our knowledge, this is the first large-scale prospective population-based study to examine the association between the Framingham CVD risk score and dementia, and certainly the first to use individual participant meta-analysis methodology.

Any mention of dementia on a death certificate resulted in a death being classified as dementia-related. This is appropriate as dementia may well not be the immediate cause of death but an important contributory factor. Classifying cause of death according to death certification is a common methodology in population-based studies. Under-reporting of dementia on death certificates seems to be improving—a recent memory clinic study found that 71.5% of 502 patients with probable Alzheimer disease had dementia correctly recorded on their death certificates [9]. Autopsy studies confirm that death certification of CVD is satisfactory for the purposes of epidemiological research [10].

None of the additional analyses essentially altered the findings of the study. However, dropping dementia-related deaths in the first two years of follow up did reduce the magnitude of the association between the Framingham CVD risk score and dementia death suggesting that part of the observed association between the risk score and dementia may relate to participants suffering from undiagnosed subclinical CVD at baseline. Approximately a third of participants (33.8%) had data missing for one or more variable necessary for calculating the Framingham CVD risk score. However, accounting for missing data by multiple imputation had little effect on the results and therefore the missing data are unlikely to have resulted in bias.

While cardiovascular disease risk factors have been linked to cognitive decline [4] and dementia risk [1], these results suggest that, importantly, the Framingham CVD risk score was no more strongly associated with future dementia than age. It therefore offers no added value in predicting dementia. Therefore, though CVD risk factors may play a role in dementia aetiology, future research attention should also focus on non-CVD risk factors and risk markers for dementia, including changes in Aβ42 levels in cerebrospinal fluid [11], metabolic alterations in PET scans [12], and possibly also biomarkers related to immune function, endocytosis and amyloid-β precursor proteins [13–15].

Funding

The Health Survey for England is part of a programme of surveys commissioned by The UK National Health Service Information Centre for health and social care, and carried out since 1994 by the Joint Health Surveys Unit of the National Centre for Social Research (NatCen) and the Department of Epidemiology and Public Health at the University College London Medical School. TCR is supported by Alzheimer Scotland and he is employed in the NHS by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). TCR and JMS are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. TCR, JMS and GDB are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged. MH is supported by the British Heart Foundation. ES is supported by a NIHR Career Development Fellowship. GDB was a Wellcome Trust Fellow during the preparation of this manuscript. MK is supported by the Medical Research Council, UK, (K013351), the US National Institutes of Health (R01HL036310; R01AG034454) and a professorial fellowship from the Economic and Social Research Council.

All researchers are independent of funders who played no role in this study.

Conflict of interest

The authors declare no conflict of interest.

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Psychological Distress as a Risk Factor for Dementia Death

Current estimates suggest that neuropsychiatric disorders account for 28% of the global burden of disease.[1] While depression and anxiety (commonly referred to as psychological distress) have been shown to be a consequence of dementia, the converse is less clear. The possibility that psychological distress might be a risk factor for dementia has major public health implications. However longitudinal studies—which are best placed to examine this relationship—have, with some exceptions,[2,3] been small in scale (affecting study precision), excluded individuals younger than 65 years (limiting insights into the pre–older age origins of dementia), or have used clinical samples (reducing generalizability). Accordingly, we examined the role of psychological distress as a risk factor for and dementia death by pooling 10 large community-based cohort studies.

Methods. Participants were recruited from the Health Survey for England,[4] an annual general population-based cross-sectional study (with a longitudinal component) representative of household-dwelling individuals in England. Results from 1994 through 2004 were pooled. Participants gave informed consent; ethical approval was obtained from the London Research Ethics Council.

Psychological distress was measured during a household visit using the 12-item General Health Questionnaire (GHQ-12), a widely used measure of psychological distress in population studies comprising items rating anxiety, depression, social dysfunction, and loss of confidence. Higher scores indicate greater distress. We used a cut off score of 4 or greater to denote psychological distress as validated against standardized psychiatric interviews.[5] Dementia was identified from death certification and coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 290.0 through 290.4 and 294.9 and *International Statistical Classification of Diseases, 10th Revision (ICD-10)* codes F01, F03, F09, and G30. Follow-up was until date of death or February 15, 2008, whichever came first.

We used Cox proportional hazards models to compute hazard ratios with accompanying 95% confidence intervals for GHQ-12 score in relation to dementia-related deaths. Study members scoring zero (no apparent distress) denoted the reference group. Models were adjusted for age, sex, occupational social class (OSC),[6] parental OSC, age at leaving full-time education, current smoking (yes/no), alcohol consumption (units per week), and existing cardiovascular disease (CVD) (yes/no), and diabetes (yes/no). Statistical analyses were conducted using PASW statistics, version 18.0 (SPSS, Chicago, Illinois), and R for Max OS X, version R-2.13.0.

Results. The initial sample included 85 261 adults (in 1996 the GHQ-12 was not used). After removing individuals who declined linkage to mortality records (n=9325) and those with missing GHQ-12 data (n=2865), the analytic sample comprised 73 071 individuals (54.8% women) with a mean (SD) age of 55.9 (14.3) years (range, 35-102 years). Data were missing for 1 or more variables in 21% (n=15 355) of the sample. Individuals with missing data were more likely to be older, be female, belong to a manual OSC, leave school later, be a nonsmoker, drink alcohol moderately, and have CVD and diabetes.

Of the 10 170 deaths during follow-up, 455 had dementia coding. A higher GHQ-12 score was associated with increased risk of dementia death in an age-adjusted model (GHQ-12 score of 1-3: HR, 1.44 [95% CI, 1.17-1.78]; GHQ-12 score of 4-12: HR, 1.74 [95% CI, 1.36-2.22]; *P* value for trend, <.001). Adding all remaining covariates (sex, OSC, parental OSC, age at leaving full-time education, current smoking, alcohol consumption, and existing CVD and diabetes) led to some attenuation of effect but statistical significance at conventional levels was retained (GHQ-12 score of 1-3: HR, 1.27 [95% CI, 1.00-1.61]; GHQ-12 score of 4-12: HR, 1.56 [95% CI, 1.17-2.07]; *P* value for trend, .005). In the **Figure** we relate 7 categories of GHQ score to dementia death to provide more detailed insight into the shape of the relationship. There was evidence of a dose-response effect (*P* value for trend, .001). Excluding individuals with any missing data (sample n=57 716; 361 dementia deaths) or dementia deaths within 5 years (sample n=72 926; 310 dementia deaths)—the latter to explore reverse causality—did not affect our results.

Comment. We found an association between elevated psychological distress and an increased risk of dementia death in a large general population sample of apparently dementia-free adults, which remained after adjustment for age, sex, OSC, education, alcohol use, smoking, and existing CVD and diabetes. Cardiovascular risk factors have been linked

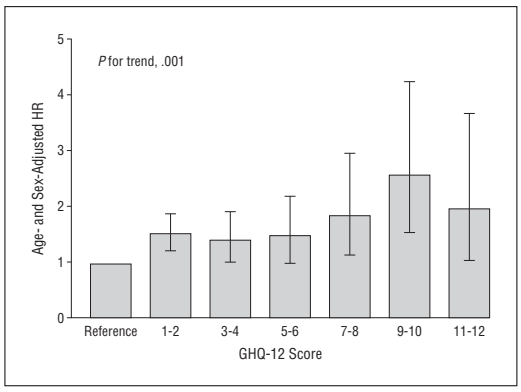

Figure. Age- and sex-adjusted hazard ratios (HRs) with 95% confidence intervals for psychological distress in relation to the risk of dementia death: the Health Surveys for England. Reference=zero score on the 12-item General Health Questionnaire (GHQ-12). Higher score indicates greater distress.

with dementia,[7] but the association found in our study remained after controlling for them, thus implicating other explanations for the gradient seen. One possibility is a toxic effect of hypercortisolemia in depression on the hippocampus.[8] Further research is required to investigate whether appropriate treatment of depression reduces dementia risk.

Tom C. Russ, MRCPsych
Mark Hamer, PhD
Emmanuel Stamatakis, PhD
John M. Starr, FRCPEd
G. David Batty, PhD

Author Affiliations: Scottish Dementia Clinical Research Network, NHS Scotland, Perth (Drs Russ and Starr); Alzheimer Scotland Dementia Research Centre (Drs Russ and Starr) and Centre for Cognitive Ageing & Cognitive Epidemiology (Drs Russ, Starr, and Batty), University of Edinburgh, Edinburgh, Scotland; Department of Epidemiology and Public Health, University College, London, England (Drs Hamer, Stamatakis, and Batty); and NHS Lothian, Edinburgh (Dr Starr).
Correspondence: Dr Russ, Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Sq, Edinburgh EH8 9JZ, Scotland (tom.russ@nhs.net).
Author Contributions: *Study concept and design:* Russ, Hamer, and Batty. *Acquisition of data:* Hamer, Stamatakis, and Batty. *Analysis and interpretation of data:* Russ, Starr, and Batty. *Drafting of the manuscript:* Russ and Batty. *Critical revision of the manuscript for important intellectual content:* Russ, Hamer, and Stamatakis, Starr, and Batty. *Statistical analysis:* Russ and Batty. *Obtained funding:* Stamatakis and Batty. *Study supervision:* Hamer, Starr, and Batty.
Financial Disclosure: None reported.
Funding/Support: Dr Russ is supported by Alzheimer Scotland and he is employed in the NHS by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). Dr Russ and Starr are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. Drs Russ, Starr, and Batty are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged. GDB is a Wellcome Trust Fellow.

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Association between psychological distress and mortality: individual participant pooled analysis of 10 prospective cohort studies

Tom C Russ *alzheimer scotland clinical research fellow*[1 2 3], Emmanuel Stamatakis *senior research associate and national institute for health research career development fellow*[4], Mark Hamer *principal research associate*[4], John M Starr *professor of health and ageing*[1 2 3 5], Mika Kivimäki *professor of social epidemiology*[4], G David Batty *reader in epidemiology/wellcome trust fellow*[3 4]

[1]Scottish Dementia Clinical Research Network, NHS Scotland, Murray Royal Hospital, Perth, UK; [2]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh EH8 9JZ, UK; [3]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh ; [4]Department of Epidemiology and Public Health, University College London, London, UK; [5]NHS Lothian, Edinburgh

Abstract

Objective To quantify the link between lower, subclinically symptomatic, levels of psychological distress and cause-specific mortality in a large scale, population based study.

Design Individual participant meta-analysis of 10 large prospective cohort studies from the Health Survey for England. Baseline psychological distress measured by the 12 item General Health Questionnaire score, and mortality from death certification.

Participants 68 222 people from general population samples of adults aged 35 years and over, free of cardiovascular disease and cancer, and living in private households in England at study baseline.

Main outcome measures Death from all causes (n=8365), cardiovascular disease including cerebrovascular disease (n=3382), all cancers (n=2552), and deaths from external causes (n=386). Mean follow-up was 8.2 years (standard deviation 3.5).

Results We found a dose-response association between psychological distress across the full range of severity and an increased risk of mortality (age and sex adjusted hazard ratio for General Health Questionnaire scores of 1-3 *v* score 0: 1.20, 95% confidence interval 1.13 to 1.27; scores 4-6: 1.43, 1.31 to 1.56; and scores 7-12: 1.94, 1.66 to 2.26; P<0.001 for trend). This association remained after adjustment for somatic comorbidity plus behavioural and socioeconomic factors. A similar association was found for cardiovascular disease deaths and deaths from external causes. Cancer death was only associated with psychological distress at higher levels.

Conclusions Psychological distress is associated with increased risk of mortality from several major causes in a dose-response pattern. Risk of mortality was raised even at lower levels of distress.

Introduction

A series of studies have shown an association between symptoms of depression and anxiety (commonly referred to as psychological distress) and an elevated risk of premature mortality,[1 2] cardiovascular disease,[3-6] and potentially all cancers,[7] although these are not universal observations.[8 9] Prospective studies investigating these associations have generally been small in scale, with only two studies reporting more than 1000 disease events.[10 11] Smaller studies lead to unreliable estimates of risk, do not permit detailed investigation of the effect of reverse causality, and hamper insights into the association across the full range of psychological distress severity. Investigation of the role of reverse causality—the possibility that the early stages of disease (for example, chest pain) might cause psychological distress—requires large numbers of participants and events to have a sufficiently large sample after individuals with existing illness or deaths in the early phases of follow-up are excluded.

Furthermore, extant studies have been unable to adequately examine whether a dose-response association exists between distress and mortality. The increased mortality associated with mental illness that is sufficiently severe to need admission to a psychiatric hospital is well described.[12] However, if the influence of psychological distress on mortality is occurring at levels

lower that hitherto suggested—in people who would not come to the attention of mental health practitioners—this may have potentially important implications for treatment.

In view of these limitations of existing studies, we undertook an individual participant meta-analysis of 10 large, community based cohort studies of the role of psychological distress as a risk factor for death from all causes, cardiovascular disease, cancer, and external causes. In contrast to a literature based meta-analysis, which may have to exclude studies not reporting their results in an appropriate manner, the possibility of publication bias is minimised in an individual participant meta-analysis through close collaboration with data providers. Furthermore, a literature based meta-analysis cannot provide precise estimates of associations between risk markers and disease, reliable information on the shape of a specific risk factor-disease relation (for example, dose-response *v* threshold), or a consistent approach to statistical control for plausible covariates and subgroup analyses. While this approach has been taken for physiological risk factors for mortality previously,[13 14] the present study is the first such meta-analysis of psychological distress.

Methods

Study samples

Participants were taken from the Health Survey for England,[15 16] a representative health examination study sampling people from the general population living in private households in that country. From 1994 to 2004, 11 independent, cross sectional studies with identical methodologies took place on an annual basis. Consenting study members (75 936 (89.1%)) were linked to National Health Service mortality data up to February 2008. For this analysis, we used raw data from people aged 35 years and over from all these study years, with the exception of 1996 when psychological distress was not measured. Ethical approval was obtained from the London Research Ethics Council.

Measurement of psychological distress

During a household visit, interviewers collected information using computer-assisted personal interviewing modules. We measured psychological distress using the 12 item version of the General Health Questionnaire (GHQ-12), a widely used measure of distress in population studies.[17 18] The GHQ-12 is generally considered to be a unidimensional scale of psychological distress,[19] consisting of items capturing symptoms of anxiety, depression, social dysfunction, and loss of confidence. Study members respond to whether a symptom is present by using a four point Likert scale ("not at all"=0, "same as usual"=0, "more than usual"=1, "much more than usual"=1). A total GHQ-12 score of four or greater leads to people being defined as psychological distress "cases" and scores 0-3 as "non-cases"; this definition has been validated against standardised psychiatric interviews and has been strongly associated with various psychological disorders such as depression and anxiety.[20 21] Most previous studies used such a dichotomy and few have examined associations across the full range of psychological distress. No standard cut-off values exist for dividing up "cases" identified by a GHQ-12 score threshold. We therefore chose to divide people into four groups based on their GHQ-12 score: asymptomatic (score 0), subclinically symptomatic (score 1-3), symptomatic (score 4-6), and highly symptomatic (score 7-12).

Mortality data

Causes of death recorded on death certificates were coded using the international classification of diseases, 9th and 10th revisions (ICD-9 and ICD-10, respectively). We identified cardiovascular disease deaths (including ischaemic heart disease, cerebrovascular disease, peripheral vascular disease and heart failure) using codes 410-414, 430-438, 440, 443-5, and 428 (ICD-9); and I20-I25, I50, I60-70, I73 and I74 (ICD-10). Cancer deaths were identified using codes 140-239 (ICD-9) and C00-D48 (ICD-10). We identified deaths from external causes using codes 800-999 and E800-E999 (ICD-9) and S00-Y98 (ICD-10). For the main analyses, any mention of a condition on the death certificate was counted but a subgroup analysis restricted cases to those where the condition was the underlying cause of death.

Statistical analyses

We ascertained that the proportional hazards assumption had not been violated by inspecting the log(−log(survival)) plot. We then used Cox proportional hazards models[22] to compute study-specific hazard ratios with accompanying 95% confidence intervals for the association of GHQ-12 score with mortality outcomes. Heterogeneity in the effect estimates between studies was examined using the I^2 statistic, which indicates the proportion of the total variation in the estimates due to between-studies variation. The I^2 varied between 0% and 81.1%, depending on the mortality outcome and psychological distress variable used in the analysis. Owing to this heterogeneity, we pooled the study-specific effect estimates and their standard errors in random effects meta-analyses. Study members scoring 0 on the GHQ-12 were regarded as being free of psychological distress and used as the reference group. We compared this group with the three GHQ-12 score groups (scores 1-3, 4-6, and 7-12), and also reported the hazard ratio per one standard deviation increment in GHQ-12 score (calculated with sex specific standard deviations: men 2.41, women 2.75).

Days were the time scale and, for participants with no record of an event, the data were censored at 15 February 2008. Models were adjusted for age (years), sex, current occupational social class (professional, managerial or technical, skilled non-manual, skilled manual, partly skilled, and unskilled), body mass index, systolic blood pressure (mm Hg), physical activity (any moderate to vigorous physical activity in a week), smoking status (not a current smoker; or <5, 5-10, 10-15, 15-20, and >20 cigarettes per day), alcohol consumption (units per week), and diabetes at baseline (yes or no). Details on the measurement protocols and data handling of these covariates can be found elsewhere.[16 23] We calculated the population proportional attributable risk for each mortality outcome and the four categories of GHQ-12 score using a standard equation.[24]

To further examine the association between crude GHQ-12 score and mortality (all cause, cardiovascular disease, cancer, and external causes), we meta-analysed study specific Cox proportional hazard models to calculate age and sex adjusted hazard ratios and 95% confidence intervals for each GHQ-12 score, with score 0 as the reference. In addition, we did a subgroup analysis to investigate potential reverse causality; analyses were repeated dropping deaths within the first five years of follow-up. This analysis did not include deaths from external causes.

We compared people with data missing for one or more variable with those with complete data. Covariates were compared with Student's *t* test for continuous variables and χ^2 tests for categorical variables. In the sensitivity analysis, we imputed

missing values for covariates with Predictive Analytics Software version 18.0,[25] using five imputations. All other analyses were conducted using R version 2.15.0[26] and the survival and metafor[27] packages. Figures were constructed using the Rmeta[28] and gplots packages. The reporting of this study conforms to the STROBE statement.[29]

Results

The initial pooled sample included 85 261 adults. Table 1⇓ shows details of individual studies. We excluded participants who declined linkage to mortality records (n=9325; web table 1 compares those who consented to record linkage with those who did not); with missing GHQ-12 data (n=2532); with baseline cardiovascular disease (n=3492), cancer (n=1511), or both (n=159); and with no cause of death recorded or for whom no survival time could be calculated (n=20). The final analytic sample comprised 68 222 people (37 649 (55.2%) women) with a mean age of 55.1 years (standard deviation 14.1, range 35-102). The composition of the sample is shown in figure 1⇓. Table 2⇓ shows details of the study members' baseline characteristics. People with higher GHQ-12 scores generally had unfavourable levels of covariates and mortality risk, apart from being slightly younger and having a lower systolic blood pressure than those with lower GHQ-12 scores. Participants with the highest GHQ-12 scores were slightly less likely to drink heavily than those with lower scores.

Of 8365 deaths during a mean follow-up of 8.2 years (standard deviation 3.5), 3382 death certificates mentioned cardiovascular disease, 2552 mentioned cancer, and 386 mentioned an external cause of death. Figure 2⇓ shows the numbers of participants, total deaths, and the number related to major causes of death. It also provides the age and sex adjusted hazard ratio for the relation of increased psychological distress (one standard deviation increase in GHQ-12 score) with overall mortality, cardiovascular disease death, cancer death, and death from external causes for each annual cohort in addition to the totals and overall effect from meta-analysis. Overall, we saw increases of 21% in age and sex adjusted risk of all cause mortality, 22% in risk of cardiovascular disease death, 9% in risk of cancer death, and 26% in risk of death from external causes per standard deviation increase in GHQ-12 score. Individually, all cohorts showed a similar effect, although the strength of the association between GHQ-12 score and mortality was somewhat weaker for 1997 and 2002—the reason for this is unclear. However, when we conducted sensitivity analyses by excluding the 1997 and 2002 cohorts from pooled analyses, the hazard ratio was unchanged. Therefore, we included participants from these surveys in the main analyses.

Deaths from all causes

We saw a significant association, across the full range of severity, between psychological distress and all cause mortality. Table 3⇓ shows the results for the four categories of GHQ-12 score; even the subclinically symptomatic group (score 1-3) had a 20% increased risk of mortality after adjusting for age and sex. This association was essentially unchanged after adjusting for a range of covariates that included occupational social class, alcohol intake, and smoking. We saw strong evidence of a dose-response effect (age and sex adjusted hazard ratio per standard deviation disadvantage in GHQ-12 score 1.21, 95% confidence interval 1.15 to 1.27; P<0.001 for trend). Figure 3⇓ shows the association between risk of death from all causes and the full range of psychological distress.

Cardiovascular disease death

Focusing on cardiovascular disease death in particular showed a similarly increased risk in association with psychological distress, again across the full range of severity; subclinically symptomatic patients were at a 29% increased risk of cardiovascular disease death (table 3). This association remained after adjustment for each covariate individually and in a model incorporating all covariates. The magnitude of the increase in risk in the fully adjusted model was little attenuated. Again, there was strong evidence of a dose-response effect (age and sex adjusted hazard ratio per standard deviation disadvantage in GHQ-12 score 1.22, 95% confidence interval 1.14 to 1.31; P<0.001 for trend) across the full range of GHQ-12 scores (fig 3).

Cancer deaths

Cancer death was not associated with low levels of psychological distress in the same way as cardiovascular disease death (table 3). However, psychological distress in highly symptomatic patients (GHQ-12 scores 6-12) was associated with a 41% increased risk of cancer death. Figure 3 confirms that this association was only present in GHQ-12 scores greater than six. Nevertheless, we saw a significant dose-response effect (age and sex adjusted hazard ratio per standard deviation disadvantage in GHQ-12 score 1.09, 95% confidence interval 1.04 to 1.13; P<0.001 for trend). This association remained after adjustment for all covariates individually and in the fully adjusted model (hazard ratio per standard deviation disadvantage in GHQ-12 score 1.05, 0.99 to 1.11, P=0.141).

Deaths from external causes

Death from external causes was also associated with psychological distress across the full range of scores; subclinically symptomatic patients were at a 29% increased risk of death from external causes (table 3). This association remained on adjustment for covariates individually and remained unchanged in the fully adjusted model. Once again, we saw strong evidence of a dose-response effect (age and sex adjusted hazard ratio per standard deviation disadvantage in GHQ-12 score 1.26, 95% confidence interval 1.14 to 1.40; P<0.001 for trend) across the full range of GHQ-12 scores (fig 3).

The population proportional attributable risk summarises the population effect of an exposure taking into account its prevalence. For the subclinically symptomatic category of psychological distress, the proportional attributable risk was 3.8% for overall mortality (fully adjusted hazard ratio 1.16), 5.8% for cardiovascular disease mortality (1.25), −1.2% for cancer mortality (0.95), and 5.4% for deaths from external causes (1.23).

Sensitivity analysis

Data were missing for one or more variables in 39.4% (n=26 860) of the sample. People with missing data were older and were more likely to be female, be overweight, have lower blood pressure, be less active, not smoke, drink alcohol within recommended limits, and have diabetes at baseline. However, they were no more likely to belong to a non-manual occupational social class (web table 2). Therefore, participants with missing data did not always have unfavourable levels of risk factors. Accounting for missing data by multiple imputation did not alter the effect sizes found (table 4⇓).

Subgroup analyses

We excluded deaths occurring within the first five years of follow-up to examine reverse causality. This subgroup analysis slightly attenuated the effect size for the association between psychological distress and all cause mortality (age and sex adjusted hazard ratio per standard deviation disadvantage in GHQ-12 score [all data] 1.21, 95% confidence interval 1.15 to 1.27, P<0.001 *v* 1.13, 1.10 to 1.17, P<0.001) and cardiovascular disease death (web table 3). The association with cancer deaths was further attenuated towards the null by excluding deaths within the first five years of follow-up (web table 3). Comparing a narrow case definition (that the condition was the underlying cause of death) and a broad case definition (that any mention of the condition on the death certificate was sufficient) had essentially no effect on the results (web table 4).

Discussion

The main finding of this study was a dose-response association between psychological distress and mortality from all causes, cardiovascular disease, and external causes across the full range of distress, even in people who would not usually come to the attention of mental health services. A similar association with cancer was only seen at higher levels of psychological distress. These associations remained after adjustment for age, sex, current occupational social class, body mass index, systolic blood pressure, physical activity, smoking, alcohol consumption, and diabetes. The associations with deaths from all causes, cardiovascular disease, and cancer remained after deaths in the first five years of follow-up were excluded.

Study strengths and limitations

This study is the first to use an individual participant meta-analysis methodology to examine the association between a psychological variable and mortality. It used a very large sample of the general population, and over 8000 participants died during follow-up. This large sample size provides sufficient power to allow detailed analyses to be conducted and reverse causality to be investigated. The cohort participants were well characterised, allowing relevant contextual variables to be incorporated into the statistical models, although the possibility of residual confounding remains.

Using GHQ-12 score to estimate psychological distress, although widely used in population based studies,[18] is not without limitations. The scale itself, with non-specific questions about feelings of unhappiness and confidence, worry, and feelings of worthlessness, does not provide a clinical diagnosis of anxiety or depression, even though the 12 items do capture several diagnostic criteria in ICD-10 or the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. However, there is evidence that screening positive on the GHQ-12, defined here as scores of 4 or more, is associated with anxiety and depression.[20 21] GHQ-12 has been shown to be a valid screening tool for anxiety and depression diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition (revised).[30]

Classifying cause of death according to death certification is a common methodology in epidemiological studies. Since causes of death are based on the certifying doctor's clinical assessment and knowledge of the deceased person, they may not always be perfectly accurate, but it is likely that the broad causes of death (for example, cardiovascular disease and cancer) used in the present study were sufficiently valid. The only study in the United Kingdom comparing death certification, with about 60 autopsy findings,[31] found that cardiac disease was correctly recorded on death certificates in all 21 cases and neoplastic disease was correctly recorded in 14 of 18 cases. Elsewhere, in Norway, analyses of 1140 autopsies showed that death certification of stroke and ischaemic heart disease was satisfactory for the purposes of epidemiological research.[32]

Another limitation in the current study was the relatively large number of participants with data missing for one or more variables. The differences between those with and without missing data, detailed above, were all highly significant, apart from current occupational social class. However, statistical significance was partly achieved as a result of the large sample size and the absolute differences are small and unlikely to be clinically significant. People with missing data were not always at an increased risk of mortality. Indeed, the sensitivity analysis using multiple multivariate imputation techniques did not alter the effect sizes reported; thus, bias resulting from the missing data was unlikely.

The diminishing magnitude of association between psychological distress and mortality with increasing duration of follow-up shown in figure 2 may reflect reverse causality. That is, undiagnosed somatic illness will be associated with both an increased prevalence of psychological distress and an increased risk of mortality. The effect of hidden somatic illness will diminish with increasing duration of follow-up as people with such conditions die, potentially resulting in the trend seen in figure 2. One specific criticism of many prospective studies considering depression as a causal factor in cardiovascular disease is that subclinical atherosclerosis is not controlled for,[33] and persistent depressive symptoms have been shown to be associated with coronary atherosclerosis.[34] While the current study did not have any direct measures of atherosclerosis, we excluded patients with overt cardiovascular disease at baseline and further exclusion of deaths within five years of follow-up reduced the possibility that our findings were driven by subclinical disease.

Comparison with other studies

One study of 4501 adults in primary care reported a dose-response association between psychological distress (measured by the GHQ-12) and overall mortality (366 deaths; GHQ-12 score 1-3: hazard ratio 1.38, 95% confidence interval 1.06 to 1.79; score 4-12: 1.71, 1.32 to 2.23), mainly due to ischaemic heart disease and respiratory diseases.[2] A smaller study (n=923) found a 16% increase in mortality per point increase in GHQ-12 score, mainly in men (hazard ratio 1.16, 1.07 to 1.25, P<0.001).[35] The Framingham Heart Study found a direct association between depressive symptoms and all cause mortality in 3634 people (hazard ratio per tertile increment on the Center for Epidemiologic Studies depression scale 1.37, 95% confidence interval 1.10 to 1.71; P=0.005 for trend).[36] In the Whitehall II study of 10 000 British civil servants, psychological distress, measured by a 30 item GHQ scale, was not associated with death from all cause mortality (355 deaths).[37] Therefore, the present study is the largest so far to show a dose-response relation between psychological distress and mortality.

The association between depression and mortality is less clear in later life, but the association remains even with adjustment for cognitive and functional impairment and social support. However, the association seems to disappear when people are followed up over long periods.[37-39] This finding is consistent with our data because the effect estimates were smallest in participants with the longest follow-up period (the earliest surveys) compared with those with shorter follow-up (more

recent surveys; fig 2). As mentioned above, this difference might relate to dilution of the effect of undiagnosed somatic illness at baseline. Changes in psychological distress during the follow-up could have attenuated associations with mortality.

As described, prospective studies investigating the association between psychological distress and cardiovascular disease have also generally been small and therefore underpowered, none reporting more than several hundred cardiovascular events.[2 4 9 40-42] However, they all found an increased risk of cardiovascular disease, one reporting a dose-response association (137 deaths from all circulatory disease; hazard ratios 1.42 and 1.66 for GHQ-12 scores 1-3 and 4-12, respectively).[2] A study looking at phobic anxiety found an age adjusted relative risk of fatal coronary heart disease of 3.01 (n=40).[34] A meta-analysis of 21 studies investigating the association between depressive symptoms and coronary heart disease incidence found a pooled relative risk of 1.81, similar for fatal and non-fatal outcomes but greater for clinically diagnosed depression than depressive symptoms.[6] A recent meta-analysis showed a pooled adjusted hazard ratio of 1.45 (95% confidence interval 1.29 to 1.63) for depression and stroke.[43] These effect estimates are similar to most published studies investigating depression or depressive symptoms as aetiological risk factors for cardiovascular disease, which generally report a relative risk of 1.5 to 2, though the Whitehall II study only identified an association in men.[42] The results of the current study, using cardiovascular disease death as the outcome of interest, are comparable to the results of this recent meta-analysis.[43]

One large retrospective study found a risk ratio of 1.39 for myocardial infarction in 12 304 participants with depression.[44] However, the absence of data for the presence of prevalent cardiovascular disease at baseline is an important limitation, particularly by comparison with the extensive baseline assessment in the Health Survey for England.

Distress in general is sometimes dismissed as a reaction to the diagnosis of a serious physical illness. In the present study, excluding deaths in the first five years of follow-up attenuated the association between psychological distress and cancer mortality, suggesting that this might partly explain the association. However, a meta-analysis of 165 studies found an association between stress related psychological factors and cancer incidence in healthy people (P=0.005).[7] In addition, chronic and severe depression is possibly associated with cancer incidence ,with a stronger association generally found with disease progression.[33]

Mechanism of effect

The mechanism of the association between psychological distress and mortality might be direct or indirect. A direct effect could be a physiological change associated with an increased risk of death. For example, acute psychological stress does alter cardiovascular physiology and is associated with transient myocardial ischaemia even in the absence of disease.[3] Furthermore, both psychological stress and depression could lead to dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in a modest increase in inflammatory markers and cortisol release.[45] Depressive symptoms are associated with altered autonomic functioning, such as 3-methoxy-phenylglycol (a major metabolite of noradrenaline) response to stressors.[41] Depressive symptoms are also associated with increased levels of inflammatory markers, including C reactive protein,[9] interleukin 6, and tumour necrosis factor α.[45] Antidepressant drugs have been shown to suppress the inflammatory response,[45] but use of these substances has been associated with increased systemic inflammation independent of comorbidity[46] and increased cardiovascular disease.[47] General population surveys show that about 3.7% of patients will have taken an antidepressant during the past year.[48] Therefore, it is unlikely that antidepressant use alone can explain the increased risk of mortality found with psychological distress.

Psychiatric illness is associated with increased mortality,[49] and part of this association could be mediated by behavioural and lifestyle factors,[50] including physical inactivity and smoking. However, we were able to incorporate many of the important behavioural and lifestyle factors into the models in the current study, and the association between psychological distress and mortality remained highly significant, suggesting that indirect mechanisms are unlikely to completely explain this association.

Implications

Depression is a serious and debilitating disorder requiring treatment in its own right, but the finding that any level of psychological distress is associated with increased mortality and an increased risk of death from cardiovascular disease, external causes, and cancer (albeit only at higher levels of distress) is highly important. Furthermore, only two studies, much smaller than the present study, have previously demonstrated a dose-response relation between psychological distress and all cause[35] or cardiovascular disease mortality,[2] with other studies having compared presence and absence of psychological distress.[4 9 40-42 46] However, due to its large sample size, the present study was able to offer detailed insight into this dose-response relation. All participants with any psychological distress, even those with low GHQ-12 scores (and therefore considered subclinically symptomatic), were at an increased risk of mortality from all causes, cardiovascular disease, and external causes. The association between psychological distress and cancer was not present in subclinically symptomatic patients. One study has identified that different aspects of distress (depression, apathy or anergia, and anxiety measured by the 30 item GHQ) have differential effects on causes of death.[46]

While the association between psychological distress and mortality has attracted a great deal of attention, little evidence indicates favourable effects, in terms of mortality, with treatment. Trial evidence has not suggested that treating depression decreases mortality in patients with existing cardiovascular disease,[51-53] but evidence from the current study of the increased risk associated with even low levels of psychological distress in the general population suggests that the overall picture may be more complex. Further research is required to investigate whether treating psychological distress, including overt depression or different aspects of distress, could have an ameliorating effect on the increased mortality demonstrated here.

Contributors: GDB conceived and designed the study. ES, MH, and GDB were responsible for acquisition of data. TCR, MK, and GDB were responsible for analysis and interpretation of data. TCR and GDB drafted the manuscript. TCR, ES, MH, JMS, MK, and GDB critically revised the manuscript for important intellectual content. TCR, ES, MK, and GDB did the statistical analysis. GDB obtained funding. MH, MK, and GDB were responsible for study supervision. TCR and GDB are the study guarantors. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

What is already known on this topic

Evidence indicates an association between symptoms of depression and anxiety (commonly referred to as psychological distress) and mortality from various major causes

However, previous studies have been underpowered and unable to reliably ascertain thresholds of risk

What this study adds

A dose-response association exists between psychological distress and major causes of mortality across the full range of distress

That a considerably raised risk of mortality was evident, even at low levels of psychological distress, should prompt research into whether treatment can modify this increased risk

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding: The study did not receive any specific funding. TCR is supported by Alzheimer Scotland and employed in the NHS by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). TCR and JMS are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. TCR, JMS, and GDB are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). The Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and United Kingdom Medical Research Council provided funding. ES is supported by a National Institute for Health Research career development fellowship. MK is supported by the UK Medical Research Council, the Academy of Finland, and the United States National Institutes of Health (R01HL036310; R01AG034454). GDB is a Wellcome Trust Fellow. All researchers are independent from the funders.

Ethical approval: Ethical approval was obtained from the London Research Ethics Council.

Data sharing: no additional data available.

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Accepted: 04 July 2012

Cite this as: *BMJ* 2012;345:e4933

Table 1| Characteristics of participants* according to individual cohort studies

	Year										
	1994	1995	1997	1998	1999	2000	2001	2002	2003	2004	Overall
Household response (%)	77	78	76	74	76	75	74	74	73	72	—
Estimated adult interview response (%)	71	73	71	69	70	68	67	67	66	66	—
No of participants	10 599	10 905	5875	11 058	5522	8684	11 283	5399	10 887	5049	85 261
Age (years)											
Mean (SD)	56.1 (14.4)	56.2 (14.3)	55.6 (14.0)	56.1 (14.3)	55.7 (14.3)	65.8 (18.5)	56.0 (14.3)	55.4 (14.4)	56.3 (14.3)	57.0 (14.3)	56.9 (15.0)
Range	35-97	35-100	35-95	35-97	35-96	35-107	35-97	35-97	35-97	35-96	35-107
Female	5824 (54.9)	5897 (54.1)	3208 (54.6)	6079 (55.0)	2998 (54.3)	5389 (62.1)	6267 (55.5)	3041 (56.3)	6056 (55.6)	2910 (57.6)	47 669 (55.9)
Non-manual occupational social class†	5555 (53.5)	5880 (55.1)	3125 (54.3)	5865 (54.3)	3030 (56.1)	3548 (55.7)	6191 (56.3)	3034 (57.7)	6090 (57.4)	2925 (59.5)	45 243 (55.8)
Current smoker	2494 (23.5)	2528 (23.2)	1369 (23.3)	2564 (23.2)	1245 (22.6)	1428 (17.7)	2431 (21.6)	1215 (22.5)	2305 (21.2)	971 (19.3)	18 550 (22.0)
Drinks more than recommended alcohol limit‡	1992 (18.8)	2132 (19.6)	1175 (20.1)	2354 (21.3)	1053 (19.2)	1134 (16.5)	2391 (21.2)	1109 (20.6)	—§	—§	13 340 (19.8)
Cardiovascular disease¶ at baseline	506 (4.8)	547 (5.0)	265 (4.5)	500 (4.5)	271 (4.9)	661 (7.6)	566 (5.0)	225 (4.2)	482 (4.4)	226 (4.5)	4249 (5.0)
Diabetes, including hyperglycaemia, at baseline	277 (2.6)	324 (3.0)	203 (3.5)	335 (3.0)	206 (3.7)	405 (4.7)	483 (4.3)	221 (4.1)	517 (4.7)	277 (5.5)	3248 (3.8)
GHQ-12 score (mean (SD))	1.5 (2.6)	1.7 (2.8)	1.5 (2.7)	1.5 (2.7)	1.7 (2.8)	1.6 (2.8)	1.3 (2.5)	1.6 (2.7)	1.3 (2.5)	1.3 (2.6)	1.5 (2.7)
Consented to mortality linkage	10 095 (95.2)	10 199 (93.5)	5529 (94.1)	10 454 (94.5)	5177 (93.8)	5926 (68.2)	9972 (88.4)	4774 (88.4)	9494 (87.2)	4316 (85.5)	75 936 (89.1)
Follow-up (years, mean (SD))	12.3 (3.2)	11.5 (2.8)	9.9 (2.1)	9.0 (1.8)	8.1 (1.6)	6.8 (1.9)	6.4 (1.0)	5.4 (0.8)	4.5 (0.6)	3.5 (0.4)	8.2 (3.5)
Deaths from any cause (no)	1873	1764	700	1206	520	987	630	250	335	100	8365
Cardiovascular disease deaths (no)**	795	719	270	480	209	391	241	109	125	43	3382
Total cancer deaths (no)	557	574	217	401	176	194	211	86	106	30	2552
Deaths from external causes (no)	68	68	29	64	19	47	44	19	23	5	386

Data are no (%) of participants unless stated otherwise. Any discrepancies in percentages are due to missing data. SD=standard deviation.

*Table represents all participants in the surveys, irrespective of consent to mortality linkage. All subsequent tables and figures represent only participants who consented to linkage and were therefore included in the present study.

†Non-manual occupational social class comprises professional, managerial or technical, and skilled non-manual classes (I-IIINM) according to the Registrar General classification.

‡Calculated using sex specific safe limits: ≤14 units per week for women and ≤21 units per week for men.

§In 2003 and 2004, alcohol intake was recorded in a different format to other years in the Health Surveys for England.

¶Including angina, myocardial infarction, and haemorrhagic or thrombotic stroke.

**Total deaths caused by cardiovascular disease, comprising ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure.

Table 2| **Baseline characteristics of study participants according to GHQ-12 score**

	GHQ-12 category (score)				Total no
	Asymptomatic (0)	Subclinically symptomatic (1-3)	Symptomatic (4-6)	Highly symptomatic (7-12)	
No of participants	41 528	16 760	5201	4733	68 222
Female	21 736 (52.3)	9680 (57.8)	3209 (61.7)	3024 (63.9)	68 222
Age (mean (SD))	55.2 (13.7)	55.3 (14.7)	54.6 (14.9)	53.3 (14.1)	68 222
Non-manual occupational social class*	23 595 (57.8)	9436 (57.6)	2806 (55.7)	2476 (53.7)	66 834
Body mass index (mean (SD))	27.1 (4.5)	27.1 (4.8)	27.2 (5.0)	27.1 (5.4)	62 640
Systolic blood pressure† (mm Hg, mean (SD))	137.8 (20.4)	136.9 (20.6)	135.3 (20.7)	134.2 (19.7)	52 224
Physical activity‡	28 215 (67.9)	10 957 (65.4)	3344 (64.3)	2868 (60.6)	68 222
Current smoker	8657 (20.9)	3890 (23.2)	1350 (26.0)	1489 (31.5)	68 191
Drinks more than recommended alcohol limit§	7172 (21.5)	2883 (20.5)	847 (19.3)	759 (19.1)	55 796
Diabetes (including hyperglycaemia)	1172 (2.8)	574 (3.4)	203 (3.9)	185 (3.9)	68 222

Data are no (%) of participants unless stated otherwise. Any discrepancies in percentages are due to missing data. SD=standard deviation.

*Non-manual occupational social class comprises professional, managerial or technical, and skilled non-manual classes (I-IIINM) according to the Registrar General classification.

†Mean of second and third readings.

‡Binary variable: any weekly moderate to vigorous physical activity.

§Calculated using sex specific safe limits: ≤14 units per week for women and ≤21 units per week for men.

Table 3| **Association between psychological distress and cause specific mortality**

Model	Deaths (no)	Participants (no)	GHQ-12 score				1 standard deviation disadvantage in GHQ-12 score*	P for trend
			0	1-3	4-6	7-12		
Total mortality								
Age and sex adjusted	8365	68 222	1 (reference)	1.20 (1.13 to 1.27)	1.43 (1.31 to 1.56)	1.94 (1.66 to 2.26)	1.21 (1.15 to 1.27)	<0.001
Fully adjusted†	4963	41 362	1	1.16 (1.08 to 1.24)	1.37 (1.23 to 1.51)	1.67 (1.41 to 2.00)	1.16 (1.12 to 1.20)	<0.001
Cardiovascular disease‡ mortality								
Age and sex adjusted	3382	68 222	1 (reference)	1.29 (1.17 to 1.43)	1.44 (1.27 to 1.62)	2.05 (1.57 to 2.70)	1.22 (1.14 to 1.31)	<0.001
Fully adjusted†	1956	41 362	1	1.25 (1.08 to 1.44)	1.45 (1.23 to 1.71)	1.72 (1.44 to 2.06)	1.17 (1.12 to 1.22)	<0.001
Cancer mortality								
Age and sex adjusted	2552	68 222	1 (reference)	0.92 (0.84 to 1.01)	1.07 (0.89 to 1.29)	1.41 (1.22 to 1.64)	1.09 (1.04 to 1.13)	<0.001
Fully adjusted†	1698	41 362	1	0.95 (0.85 to 1.07)	1.05 (0.85 to 1.30)	1.29 (1.04 to 1.61)	1.05 (0.99 to 1.11)	0.141
External cause mortality								
Age and sex adjusted	386	68 222	1 (reference)	1.29 (1.01 to 1.65)	1.93 (1.31 to 2.83)	2.34 (1.52 to 3.60)	1.26 (1.14 to 1.40)	<0.001
Fully adjusted†	241	41 362	1	1.23 (0.90 to 1.70)	2.07 (1.33 to 3.21)	3.19 (1.78 to 5.70)	1.32 (1.13 to 1.55)	0.001

Data are hazard ratio (95% confidence interval) unless indicated otherwise.

*GHQ-12 score standardised with sex specific standard deviations.

†Model adjusted for age, sex, occupational social class, diabetes, body mass index, systolic blood pressure, physical activity, smoking, and alcohol consumption.

‡Cardiovascular disease comprises ischaemic heart disease, stroke, peripheral vascular disease, and heart failure.

Table 4| **Sensitivity analysis of association between psychological distress and cause specific mortality, with and without multiple imputation**

	Meta-analysis			Multiple imputation		
Fully adjusted model* by cause of death	**Deaths (no)**	**Participants (no)**	**1 standard deviation disadvantage in GHQ-12 score†**	**Deaths (no)**	**Participants (no)‡**	**1 standard deviation disadvantage in GHQ-12 score†**
Total	4963	41 362	1.16 (1.12 to 1.20)	8492	57 861	1.15 (1.13 to 1.18)
Cardiovascular disease§	1956	41 362	1.17 (1.12 to 1.22)	3440	57 861	1.14 (1.10 to 1.19)
Cancer	1698	41 362	0.95 (0.85 to 1.07)	2530	57 861	1.05 (1.01 to 1.09)
External cause	241	41 362	1.32 (1.13 to 1.55)	381	57 861	1.23 (1.11 to 1.36)

Data are hazard ratio (95% confidence interval) unless indicated otherwise.

*Model adjusted for age, sex, occupational social class, diabetes, body mass index, systolic blood pressure, physical activity, smoking, and alcohol consumption.

†GHQ-12 score standardised with sex specific standard deviations.

‡Total no of participants in multiple imputation models excludes the 2003 and 2004 cohort studies since they were excluded from all fully adjusted models owing to their recording of alcohol consumption in a different format to other years.

§Cardiovascular disease comprises ischaemic heart disease, stroke, peripheral vascular disease, and heart failure.

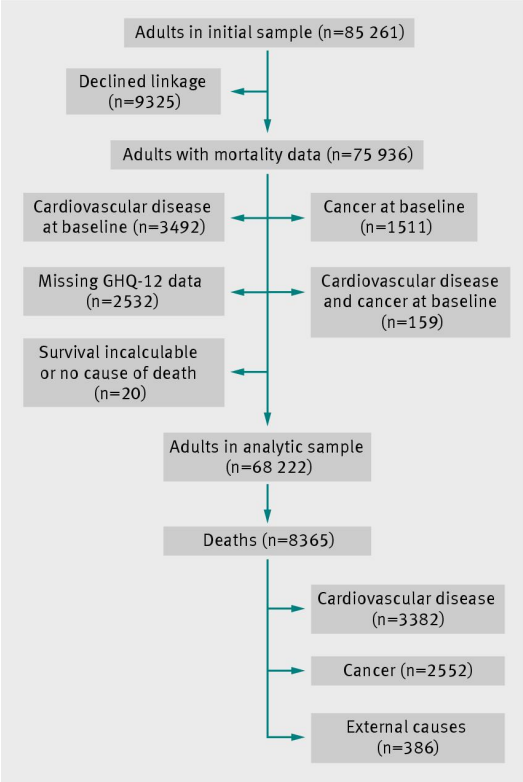

Fig 1 Flow chart of participants from initial pooled sample to analytic sample showing subsequent mortality

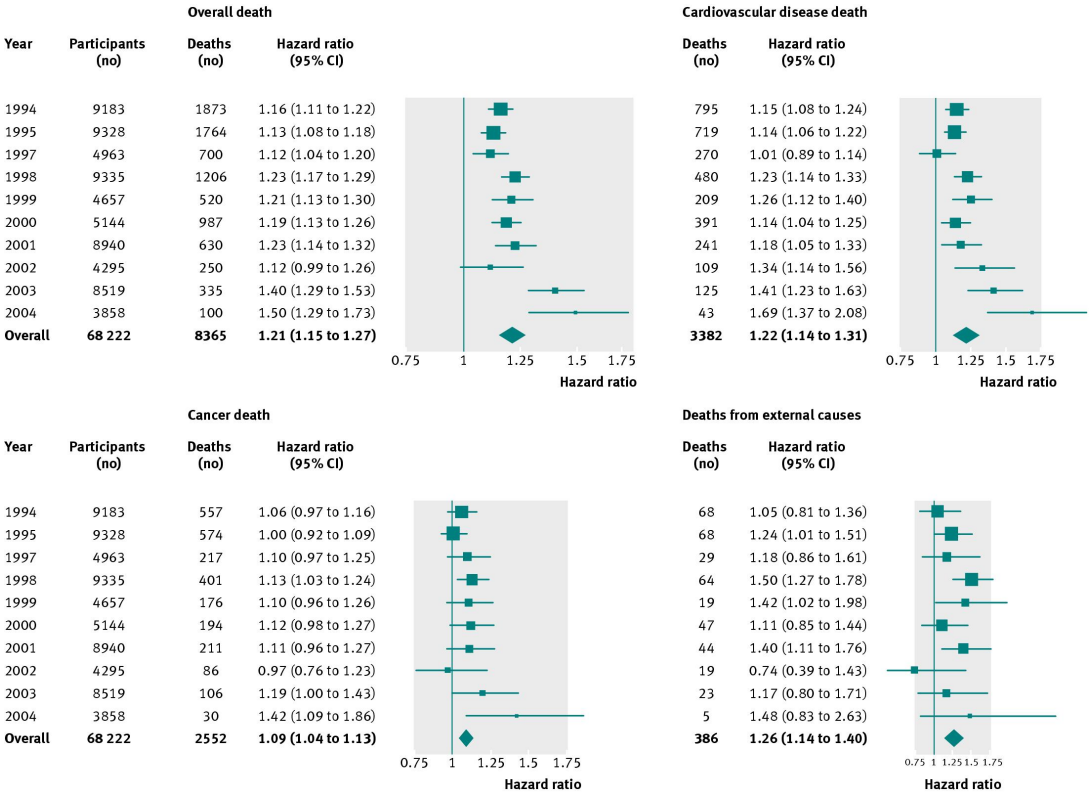

Fig 2 Number of participants, total mortality, and deaths plus age and sex adjusted hazard ratios (95% confidence intervals) per standard deviation disadvantage in GHQ-12 score, by survey year and cause of death

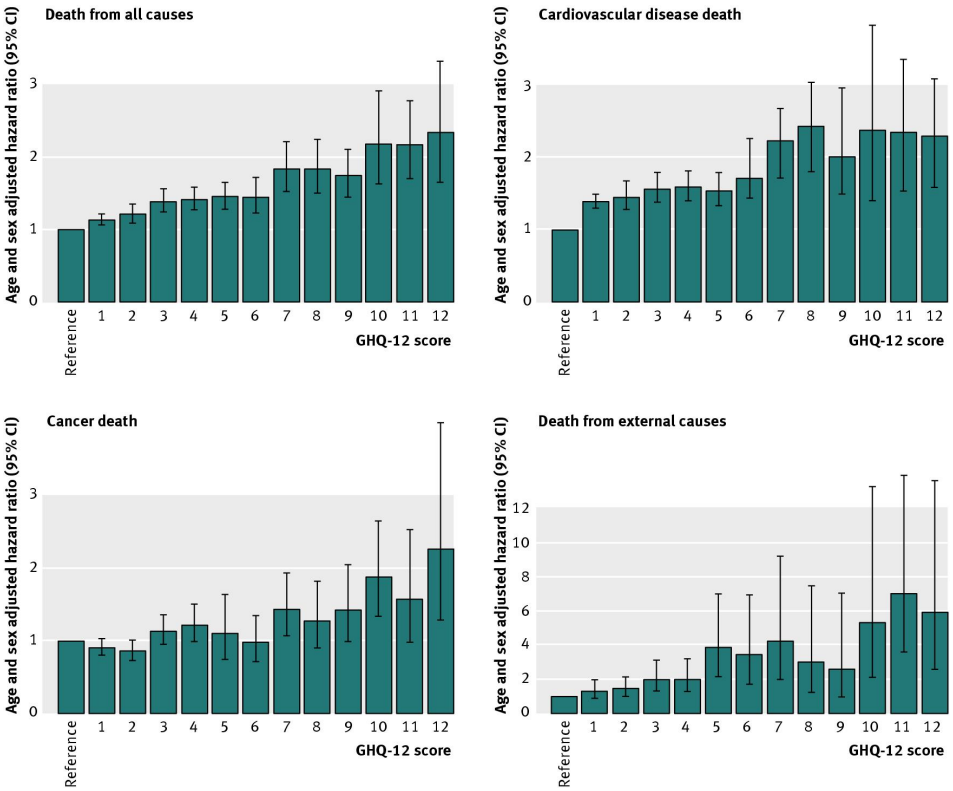

Fig 3 Association between psychological distress (GHQ-12 score) and risk of cause specific death (age and sex adjusted hazard ratio (95% confidence interval)). Reference=GHQ-12 score 0; higher GHQ-12 score indicates greater distress

Appendix Table 1. Survey participants who consented and did not consent to record linkage: follow-up of ten cohort studies from the Health Survey for England (*N* = 68,222)

Covariate	*Consented*	*Did not consent*	*p*
N	75936	9325	
Age (mean, SD)	56.1 (14.4)	64.7 (17.7)	<0.001
Female (%)	54.9	64.2	<0.001
Individual occupational social class (% I-IIINM)	56.4	52.2	<0.001
Body mass index (kg/m^2; mean, SD)	27.2 (4.7)	27.0 (4.8)	0.001
Systolic blood pressure[1] (mmHg, mean, SD)	137.6 (20.6)	136.9 (21.3)	0.096
Physical activity[2] (%)	65.3	71.4	<0.001
Current smoker (%)	22.3	18.9	<0.001
Drinks more than recommended alcohol limit[3] (%)	16.6	8.2	<0.001
Cardiovascular disease[4] (%)	4.8	6.4	<0.001
Cancer (%)	2.2	2.6	0.008
Diabetes (%)	3.7	4.8	<0.001

[1] Mean of 2nd and 3rd readings
[2] Binary variable: any weekly moderate to vigorous physical activity
[3] Calculated using sex-specific safe limits: ≤14 units per week for women and ≤21 units for men
[4] Including angina, myocardial infarction and haemorrhagic or thrombotic stroke

Appendix Table 2. Survey participants included and excluded from fully-adjusted model: follow-up of ten cohort studies from the Health Survey for England (*N* = 68,222)

Covariate	*Complete data for all variables*	*Missing data in ≥1 variable*	*p*
N	41362	26860	
Age (mean, SD)	54.1 (13.4)	56.5 (15.0)	<0.001
Female (%)	53.3	58.1	<0.001
Individual occupational social class (% I-IIINM)	57.3	58.0	0.355
Body mass index (kg/m^2; mean, SD)	27.0 (4.6)	27.4 (4.9)	<0.001
Systolic blood pressure[1] (mmHg, mean, SD)	137.7 (20.2)	135.1 (21.1)	<0.001
Physical activity[2] (%)	72.3	57.6	<0.001
Current smoker (%)	23.0	22.0	0.001
Drinks more than recommended alcohol limit[3] (%)	21.8	9.9	<0.001
Diabetes (%)	2.7	3.9	<0.001

[1] Mean of 2nd and 3rd readings
[2] Binary variable: any weekly moderate to vigorous physical activity
[3] Calculated using sex-specific safe limits: ≤14 units per week for women and ≤21 units for men

Appendix Table 3. Sub-group analysis—excluding deaths within five years of follow-up: follow-up of ten cohort studies from the Health Survey for England (*N* = 68,222)

Basic model adjusted for age and sex	*Deaths*	*n*	*1 SD disadvantage in GHQ-12 score*[1] *HR*	*p (trend)*
Total mortality				
All deaths	8365	68222	1.21 (1.15, 1.27)	<0.001
Deaths of individuals who survived >5 years	4011	55845	1.13 (1.10, 1.17)	<0.001
Cardiovascular disease mortality				
All deaths	3382	68222	1.22 (1.14, 1.31)	<0.001
Deaths of individuals who survived >5 years	1574	55845	1.17 (1.10, 1.24)	<0.001
Cancer mortality				
All deaths	2552	68222	1.09 (1.04, 1.13)	<0.001
Deaths of individuals who survived >5 years	1253	55845	1.03 (0.97, 1.09)	0.359

[1] GHQ-12 score standardised with sex-specific standard deviations
[2] Cardiovascular disease comprises ischaemic heart disease, stroke, peripheral vascular disease, and heart failure

Appendix Table 4. Sub-group analysis—Hazard ratios (95% confidence interval) for the association of psychological distress with cause-specific mortality with broad and narrow definitions[1] of disease: follow-up of ten cohort studies from the Health Survey for England (*N* = 68,222)

	Broad case definition[1]		**Narrow case definition[1]**	
	Deaths	*1 SD disadvantage in GHQ-12 score[2]* *HR*	*Deaths*	*1 SD disadvantage in GHQ-12 score[2]* *HR*
Cardiovascular disease[3] mortality				
Age- & sex-adjusted	3382	1.23 (1.14, 1.33)	2585	1.21 (1.12, 1.30)
Cancer mortality				
Age- & sex-adjusted	2552	1.09 (1.05, 1.14)	2329	1.07 (1.03, 1.12)
External cause mortality				
Age- & sex-adjusted	386	1.26 (1.14, 1.40)	201	1.28 (1.13, 1.44)

[1] Broad definition indicates any mention of the condition on the death certificate; narrow definition indicates that the condition was the underlying cause of death
[2] GHQ-12 score standardised with sex-specific standard deviations
[3] Cardiovascular disease comprises ischaemic heart disease, stroke, peripheral vascular disease, and heart failure

Socioeconomic status as a risk factor for dementia death: individual participant meta-analysis of 86 508 men and women from the UK*

Tom C. Russ, Emmanuel Stamatakis, Mark Hamer, John M. Starr, Mika Kivimäki and G. David Batty

Background
Life-course socioeconomic factors may have a role in dementia aetiology but there is a current paucity of studies. Meta-analyses of individual participant data would considerably strengthen this evidence base.

Aims
To examine the association between socioeconomic status in early life and adulthood with later dementia death.

Method
Individual participant meta-analysis of 11 prospective cohort studies (1994–2004, $n = 86\,508$).

Results
Leaving full-time education at an earlier age was associated with an increased risk of dementia death in women (fully adjusted hazard ratio (HR) for age $\leqslant 14$ *v.* age $\geqslant 16$: HR = 1.76, 95% CI 1.23–2.53) but not men. Occupational social class was not statistically significantly associated with dementia death in men or women.

Conclusions
Lower educational attainment in women was associated with an increased risk of dementia-related death independently of common risk behaviours and comorbidities.

Declaration of interest
None.

Socioeconomic inequalities in cardiovascular disease[1] and selected cancers[2] are well recognised. More recently, research attention has focused on such differentials in mental health, including depression[3] and other common mental disorders such as dementia.[4–6] There is a suggestion that socioeconomic factors may have a role in the aetiology of dementia including lifetime manual occupation[7] as well as various indicators of socioeconomic status in early life[8] and lower educational attainment.[8,9] However, because of the paucity of large-scale, well-characterised studies, the extant evidence is discordant and there has been inconsistent control for confounding variables. Thus, the precise nature of the socioeconomic status–dementia relationship remains unclear. Although individual studies undoubtedly have value in improving this evidence base, the pooling of raw data from multiple studies, which would also represent an important technical advance in this context, has yet to be utilised. We therefore undertook the first individual participant meta-analysis using data from 11 large, community-based cohort studies that held data on socioeconomic status, covariates and dementia death. The purpose of this paper is twofold: first, as a proof of principle that this methodology can be applied to the study of the role of socioeconomic position in the risk of dementia; and second, to add to the evidence base by further investigating the association between socioeconomic factors and dementia-related death.

Method

Study samples

Participants were taken from the Health Survey for England,[10] a representative general population-based health examination study sampling individuals living in households in England. From 1994 to 2004, 11 independent, cross-sectional studies with identical methodologies were conducted on an annual basis. Consenting study members (89.6%) were followed up by linkage to the UK National Health Service mortality registry. Study participants gave full informed consent and ethical approval was obtained from the London Research Ethics Council.

Assessment of socioeconomic status

During a household visit, interviewers collected information using computer-assisted personal interviewing modules. Information on occupational social class was collected during the interview and coded according to the Registrar General classification (professional (I), intermediate (II), skilled non-manual (IIINM), skilled manual (IIIM), part-skilled (IV) and unskilled (V)), a standard approach in the UK.[11] Age on leaving full-time education was recorded as <15, 15, 16, 17, 18, >18, never went to school and still in full-time education. For this study occupational social class was coded into four groups: professional/intermediate (the referent), skilled non-manual, skilled manual and part-skilled/unskilled. Educational attainment was coded into three groups: 14 years or younger, 15 years old and 16 years or older (the referent).

Assessment of other risk factors and comorbidities

Smoking status (not a current smoker; <5 per day; 5–10 per day; 10–15 per day; 15–20 per day; >20 per day), weekly alcohol consumption (converted to units of alcohol), and history of cardiovascular disease and diabetes (including hyperglycaemia) were collected by self-report at interview. Individuals drinking above safe limits of alcohol were identified using gender-specific safe limits ($\leqslant 14$ units per week for women and $\leqslant 21$ units per week for men).[12]

Psychological distress was measured using the 12-item version of the General Health Questionnaire (GHQ-12), a widely used measure in population studies.[13] A score of four is often used as a threshold to denote psychological distress,[14] but since we have previously shown that even low levels of psychological distress – that is, scores below four – are associated with an increased risk

*Preliminary results from this study were presented as a poster at the 2011 Alzheimer's Association International Conference in Paris.

of dementia in these cohort studies,[15] we adjusted for total GHQ-12 score as a continuous variable.

Ascertainment of dementia

Causes of death recorded on death certificates were coded using ICD-9[16] and ICD-10.[17] Any mention of dementia death was identified using codes 290.0–290.4, 294.9, 331.0–331.2, and 331.9 for ICD-9, and F01, F03, F09, G30 and G31 for ICD-10.

Statistical analyses

We ascertained that the proportional hazards assumption had not been violated by inspecting the log(–log(survival)) plot. We then used Cox proportional hazards models[18] to compute study-specific hazard ratios with accompanying 95% confidence intervals for the association between the measures of socio-economic status and dementia death. Heterogeneity in the effect estimates between studies was examined using the I^2 statistic, which indicates the proportion of the total variation in the estimates that is due to between-studies variation. It varied between 0% and 36.9% depending on the measure of socio-economic status used in the analysis. To obtain a conservative estimate, we pooled the study-specific effect estimates and their standard errors in random effects meta-analyses. Calendar time (days) was the time scale; for participants with no record of an event, the data were censored at the 15 February 2008.

Models were initially unadjusted, then a series of variables were added to the multivariable model: age, smoking status, alcohol consumption (units per week), baseline cardiovascular disease (yes/no), diabetes (yes/no), psychological distress (GHQ-12 score), occupational social class and educational attainment. Since, as described, the association between socioeconomic status and dementia has been reported to be different in men and women,[19] gender-specific analyses were conducted. We compared the effects of controlling for different covariates/mediators on the magnitude of the association by examining a change in the size of hazard ratio rather than a change in significance level.[20]

Individuals with data missing for one or more variables and those with no missing data were compared using Student's *t*-test for continuous variables and χ^2 tests for categorical variables. The main analysis was based on participants with no missing data. In the sensitivity analysis, missing values for covariates were imputed with PASW statistics version 18.0 for Windows using five imputations based on maximum likelihood estimates. All other analyses were conducted using R version 2.15.0 for Windows and the survival and metafor[21] packages. The reporting of this study conforms to the STROBE statement.[22]

Results

The initial sample comprised 96 605 individuals. The derivation of the sample is shown in Fig. 1. After removing individuals who declined linkage to mortality records ($n = 10\,065$) and for whom survival was incalculable or who had no cause of death recorded ($n = 32$) the maximum analytic sample comprised 86 508 people (mean age 56.1 years, s.d. = 14.4): 39 125 men and 47 383 women. Data were missing for occupational social class for 2325 individuals (analytic $n = 84\,183$) and for educational attainment for 61 individuals (analytic $n = 86\,447$). Table 1 shows the characteristics of study members from the 11 cohorts and pooled summaries.

Table 2 shows the baseline characteristics of the pooled sample according to occupational social class separately in men and women. Individuals from a lower occupational social class were older, were more likely to smoke, and had a somewhat greater likelihood of baseline cardiovascular disease, diabetes and

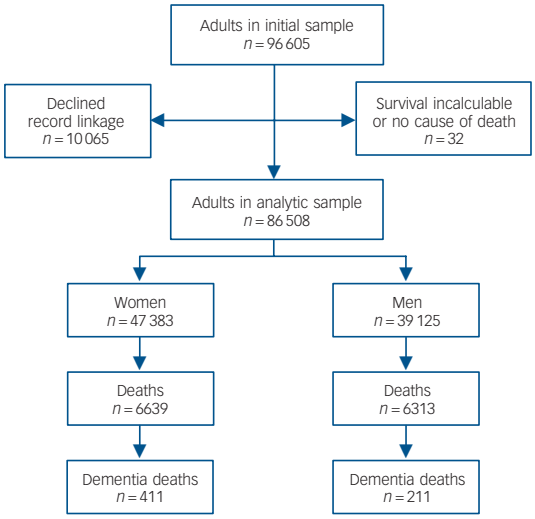

Fig. 1 Flow chart of participants from initial pooled sample through to analytic sample showing subsequent mortality: the Health Survey for England 1994–2004.

psychological distress. There was little association between occupational social class and alcohol consumption. Individuals from a lower occupational social class were more likely, as anticipated, to have spent less time in full-time education (women $r = 0.41$, $P < 0.001$; men $r = 0.43$, $P < 0.001$). Similar patterns of association were seen with education as the exposure of interest (results not shown but available from the authors on request).

Of the 12 952 deaths during a mean follow-up of 8.6 years (s.d. = 3.5), 622 were ascribed to dementia. Figures 2 and 3 show the fully adjusted hazard ratios for the association of occupational social class and educational attainment respectively, with dementia death for each cohort study, in addition to gender- specific totals and meta-analysed effects. Overall, relative to study members from professional/intermediate occupational social classes, there was no increase in the risk of dementia death among those belonging to the lower social classes in women (fully adjusted hazard ratio (HR) for skilled non-manual: HR = 0.88 (95% CI 0.59–1.31); skilled manual: HR = 0.61 (95% CI 0.36–1.06); semi-skilled and unskilled manual: HR = 0.92 (95% CI 0.62–1.36)) or men (skilled non-manual: HR = 1.03 (95% CI 0.53–2.00); skilled manual: HR = 1.03 (95% CI 0.63–1.69); semi-skilled/unskilled manual: HR = 1.33 (95% CI 0.80–2.21), Fig. 2). Relative to study members who left school aged 16 or older, there was an increase in the risk of dementia death among those leaving school earlier in women (leaving school aged 15: HR = 1.64 (95% CI 1.02–2.65); leaving school aged 14 or younger: HR = 1.76 (95% CI 1.23–2.53)) but not in men (leaving school aged 15: HR = 0.98 (95% CI 0.51–1.88); leaving school aged 14 or younger: HR = 1.20 (95% CI 0.77–1.87), Fig. 3).

Table 3 shows the impact of controlling for covariates on the association between the two indicators of socioeconomic status and dementia in women and men. The association between occupational social class and dementia death seen in age-adjusted models was completely explained by covariates in women but was more robust to statistical adjustment in men. The association between leaving full-time education at an earlier age and later dementia death observed in the age-adjusted models was fully

Table 1 Characteristics of participants[a] according to cohort study: the Health Survey for England 1994–2004

Characteristic	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	Overall
n	10 599	10 905	11 344	5875	11 058	5522	8684	11 283	5399	10 887	5049	96 605
Household response, %	77	78	79	76	74	76	75	74	74	73	72	–
Estimated adult interview response, %	71	73	75	71	69	70	68	67	67	66	66	–
Age, years												
Mean (s.d.)	56.1 (14.4)	56.2 (14.3)	56.0 (14.3)	55.6 (14.0)	56.1 (14.3)	55.7 (14.3)	65.8 (18.5)	56.0 (14.3)	55.4 (14.4)	56.3 (14.3)	57.0 (14.3)	56.9 (15.0)
Range	35–97	35–100	35–102	35–95	35–97	35–96	35–107	35–97	35–97	35–97	35–96	35–107
Female, %	54.9	54.1	54.3	54.6	55.0	54.3	62.1	55.5	56.3	55.6	57.6	55.7
Occupational social class I–IIINM, %	53.8	55.3	55.2	54.8	54.6	56.5	56.4	56.6	57.8	57.7	59.7	53.2
Current smoker, %	23.5	23.2	24.2	23.3	23.2	22.6	17.7	21.6	22.5	21.2	19.3	22.2
Drinks more than recommended alcohol limit,[b] %	18.8	19.6	20.1	20.0	21.3	19.1	13.1	21.2	20.5	–	–	19.4
Cardiovascular disease at baseline,[c] %	4.8	5.0	4.9	4.5	4.5	4.9	7.6	5.0	4.2	4.4	4.5	5.0
Diabetes (including hyperglycaemia) at baseline, %	2.6	3.0	3.1	3.5	3.0	3.7	4.7	4.3	4.1	4.7	5.5	3.7
GHQ-12 score,[d] mean (s.d.)	1.5 (2.6)	1.7 (2.8)	–	1.5 (2.7)	1.5 (2.7)	1.7 (2.8)	1.6 (2.8)	1.3 (2.5)	1.6 (1.7)	1.3 (2.5)	1.3 (2.6)	1.5 (2.7)
Consented to mortality linkage, %	95.2	93.5	93.5	94.1	94.5	93.8	68.2	88.4	88.4	87.2	85.5	89.6
Follow-up, years: median	13.5	12.5	11.5	10.5	9.5	8.5	7.4	6.6	5.6	4.6	3.5	8.4
Deaths from any cause, *n*	2320	2193	2023	892	1591	697	1364	867	337	503	165	12 952
Dementia deaths, *n*	106	104	88	43	83	30	101	34	11	17	5	622

I–IIINM, professional (I), intermediate (II) and skilled non-manual (IIINM).
a. All participants in the surveys are represented in this table, irrespective of consent to mortality linkage. All subsequent tables and figures only represent individuals who consented to linkage and were therefore included in the present study.
b. Calculated using gender-specific safe limits: ⩽14 units per week for women and ⩽21 units for men. Alcohol intake was recorded in a different format to other years in the Health Surveys for England in 2003 and 2004 and data are not included for these years.
c. History of cardiovascular disease including angina, myocardial infarction or stroke (haemorrhagic or thrombotic).
d. The General Health Questionnaire (GHQ-12) was not administered in the Health Survey for England in 1996.

Table 2 Study members' baseline characteristics according to occupational social class: the Health Survey for England 1994–2004

	Occupational social class						Total, *n*
	I	II	IIINM	IIIM	IV	V	
Women							
n	754	11 663	15 956	4079	8954	4081	45 487
Age, years: mean (s.d.)	49.1 (12.5)	53.4 (13.7)	56.0 (14.4)	59.0 (15.3)	56.6 (14.6)	60.8 (14.6)	45 487
Left school <16 years, %	4.4	23.7	43.2	65.8	63.7	39.6	45 455
Current smoker, %	12.1	18.0	19.9	26.8	28.2	29.7	45 469
Drinks more than recommended alcohol limit,[a] %	19.1	15.7	12.9	9.7	8.6	7.8	37 752
Cardiovascular disease at baseline,[b] %	1.6	2.7	3.5	5.1	4.9	6.4	45 487
Diabetes (including hyperglycaemia) at baseline, %	0.9	2.1	2.6	4.2	3.5	4.2	45 487
GHQ-12 score,[c] mean (s.d.)	1.5 (2.7)	1.6 (2.7)	1.5 (2.7)	1.8 (2.9)	1.8 (2.9)	1.8 (3.0)	38 162
Men							
n	2987	12 272	3759	12 835	5163	1680	38 696
Age, years: mean (s.d.)	54.7 (13.5)	54.3 (13.5)	56.2 (14.6)	56.4 (13.9)	56.7 (14.1)	57.2 (13.7)	38 696
Left school <16 years, %	11.5	27.8	40.0	64.1	64.2	71.4	38 667
Current smoker, %	9.2	16.1	19.8	28.6	31.2	37.6	38 672
Drinks more than recommended alcohol limit,[1a] %	22.8	25.7	21.1	23.0	20.6	22.8	32 554
Cardiovascular disease at baseline,[b] %	2.8	4.5	6.4	6.8	6.7	6.7	38 696
Diabetes (including hyperglycaemia) at baseline, %	2.7	4.0	4.8	4.6	5.4	4.5	38 696
GHQ-12 score,[c] mean (s.d.)	1.1 (2.2)	1.2 (2.3)	1.2 (2.4)	1.3 (2.5)	1.5 (2.7)	1.6 (2.9)	32 560

I, professional; II, intermediate, IIINM, skilled non-manual; IIIM, skilled manual; IV, part skilled; and V, unskilled.
a. Calculated using gender-specific safe limits: ⩽14 units per week for women and ⩽21 units for men. Alcohol intake was recorded in a different format to other years in the Health Surveys for England in 2003 and 2004 and data are not included for these years.
b. History of cardiovascular disease including angina, myocardial infarction or stroke (haemorrhagic or thrombotic).
c. The General Health Questionnaire (GHQ-12) was not administered in the Health Survey for England 1996.

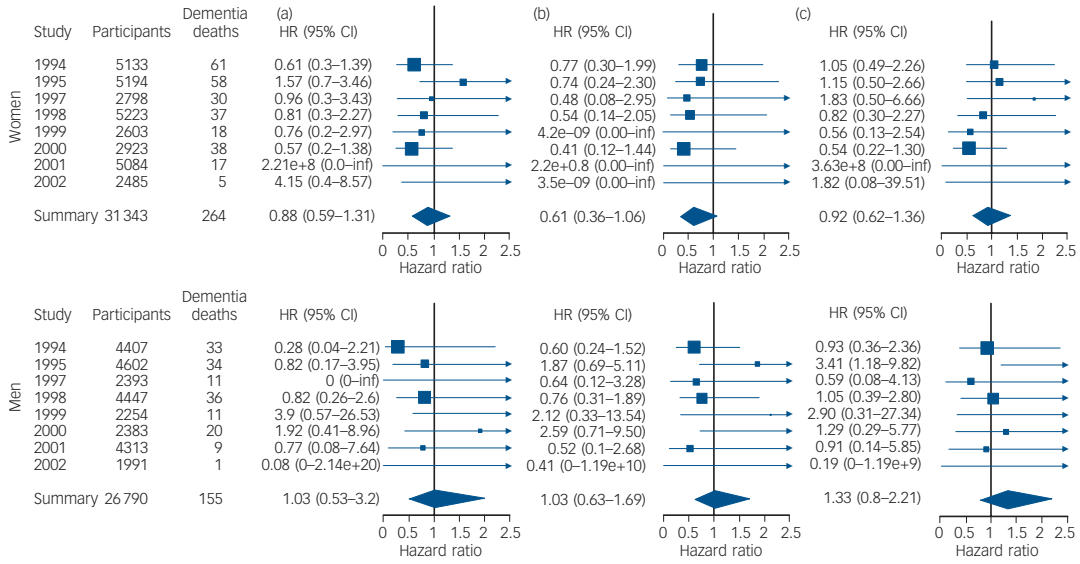

Fig. 2 Fully adjusted hazard ratios (HRs) with 95% confidence intervals of dementia death by survey year for individuals, from left to right, from (a) skilled non-manual, (b) skilled manual and (c) semi-skilled/unskilled manual occupational social classes compared with professional/intermediate: the Health Survey for England 1994–2004.

For women: I^2 values for these models are 4.1%, 0.0% and 0.0%. For men: I^2 values for these models are 0.0%, 12.9% and 6.4%.

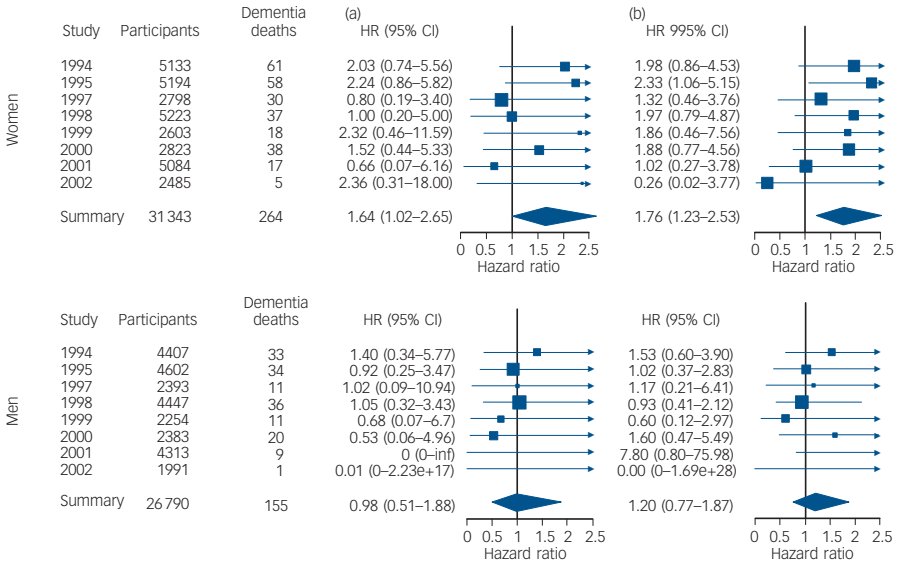

Fig. 3 Fully adjusted hazard ratios (HRs) with 95% confidence intervals of dementia death by survey year for individuals who left full-time education aged, from left to right, (a) 15 years and (b) 14 years or younger compared with those who left full-time education aged 16 years or older: the Health Survey for England 1994–2004.

For women: I^2 values for these models are 0.0% and 0.0%. For men: I^2 values for these models are 0.0% and 0.0%.

attenuated on adjustment for covariates in men but remained in women.

Sensitivity and subgroup analyses

Data were missing for one or more variables in 32.8% ($n = 28\,375$) of the sample. Online Table DS1 shows a comparison of the characteristics of individuals with complete data for all variables *v.* individuals who were missing data for one or more variables. Individuals with complete data were more likely to be male, younger, drink more alcohol per week and were more likely to drink over the recommended limits and a larger proportion were current smokers. They were less likely to have diabetes and

Table 3 Hazard ratio (95% confidence interval) for the association between occupational social class and educational attainment with dementia death: Health Survey for England 1994–2004

	Occupational social class										Age on leaving full-time education									
	Dementia deaths	*n*	I–II		IINM		IIM		IV–V		Dementia deaths	*n*	⩾16		15		⩽14			
			HR		HR (95% CI)	I^2	HR (95% CI)	I^2	HR (95% CI)	I^2			HR		HR (95% CI)	I^2	HR (95% CI)	I^2		
Women																				
Unadjusted model	358	45 487	1	(ref)	1.34 (0.97–1.86)	0.0	2.27 (1.49–3.44)	0.0	2.18 (1.59–2.98)	0.0	411	47 351	1	(ref)	1.32 (0.90–1.95)	5.4	9.87 (7.67–12.7)	0.0		
Adjusted for age (basic model)	358	45 487	1		1.05 (0.75–1.48)	5.9	0.96 (0.63–1.47)	0.0	1.33 (0.97–1.83)	0.0	411	47 351	1		1.54 (0.96–2.47)	28.4	1.61 (1.25–2.08)	0.0		
+ risk factors[a]	343	37 998	1		1.07 (0.75–1.53)	8.5	0.94 (0.61–1.46)	0.0	1.30 (0.94–1.79)	0.0	393	39 612	1		1.46 (0.88–2.43)	36.9	1.56 (1.18–2.07)	6.6		
+ somatic comorbidities[b]	358	45 487	1		1.05 (0.74–1.49)	8.5	0.96 (0.63–1.46)	0.0	1.34 (0.98–1.84)	0.0	411	47 351	1		1.57 (0.98–2.53)	29.3	1.65 (1.28–2.13)	0.0		
+ psychological distress	275	38 553	1		0.99 (0.69–1.43)	0.0	0.81 (0.49–1.35)	0.0	1.23 (0.86–1.75)	0.0	317	40 035	1		1.60 (1.04–2.48)	3.3	1.61 (1.20–2.16)	0.0		
+ age on leaving full-time education	358	45 487	1		0.93 (0.67–1.31)	2.7	0.74 (0.48–1.15)	0.0	1.01 (0.72–1.42)	0.0	–	–	–		–	–	–	–		
+ occupational social class	–	–	–		–	–	–	–	–	–	358	45 465	1		1.57 (1.02–2.43)	6.2	1.68 (1.24–2.28)	0.0		
Fully adjusted	264	31 343	1		0.88 (0.59–1.31)	4.1	0.61 (0.36–1.06)	0.0	0.92 (0.62–1.36)	0.0	264	31 343	1		1.64 (1.02–2.65)	0.0	1.76 (1.23–2.53)	0.0		
Men																				
Unadjusted model	210	36 880	1	(ref)	1.51 (0.88–2.59)	0.0	1.43 (0.95–2.15)	21.8	1.81 (1.23–2.67)	4.3	211	37 263	1	(ref)	0.77 (0.44–1.33)	0.0	8.89 (6.38–12.4)	0.0		
Adjusted for age (basic model)	210	36 880	1		1.13 (0.66–1.94)	0.0	1.29 (0.88–1.89)	11.5	1.52 (1.01–2.29)	10.3	211	37 263	1		1.03 (0.59–1.80)	0.0	1.44 (1.03–2.02)	0.0		
+ risk factors[a]	204	32 596	1		1.07 (0.62–1.85)	0.0	1.29 (0.85–1.95)	19.8	1.38 (0.86–2.22)	24.8	205	32 939	1		0.96 (0.54–1.72)	0.0	1.30 (0.92–1.84)	0.0		
+ somatic comorbidities[b]	210	36 880	1		1.14 (0.66–1.96)	0.0	1.28 (0.86–1.90)	16.8	1.49 (0.97–2.30)	16.4	211	37 263	1		1.05 (0.60–1.84)	0.0	1.38 (0.99–1.94)	0.0		
+ psychological distress	158	30 899	1		1.15 (0.60–2.19)	0.0	1.24 (0.83–1.85)	1.3	1.72 (1.12–2.64)	0.0	158	31 215	1		1.05 (0.56–1.97)	0.0	1.45 (0.98–2.14)	0.0		
+ age on leaving full-time education	210	36 854	1		1.06 (0.61–1.84)	0.0	1.12 (0.72–1.74)	20.8	1.38 (0.90–2.12)	6.1	–	–	–		–	–	–	–		
+ occupational social class	–	–	–		–	–	–	–	–	–	210	36 854	1		0.94 (0.53–1.67)	0.0	1.29 (0.88–1.88)	0.0		
Fully adjusted	155	26 790	1		1.03 (0.53–2.00)	0.0	1.03 (0.63–1.69)	13.0	1.33 (0.80–2.21)	6.4	155	26 790	1		0.98 (0.51–1.89)	0.0	1.20 (0.77–1.87)	0.0		

I–II, professional and intermediate; IINM, skilled non-manual; IIM, skilled manual; IV–V, part skilled and unskilled.
a. Risk factors comprise smoking and alcohol consumption. b. Somatic comorbidities comprise cardiovascular disease and diabetes.

cardiovascular disease at baseline. A slightly larger proportion of individuals with complete data belonged to a non-manual occupational social class and women were less likely to have left school early (the reverse was true of men). Therefore, individuals with missing data did not always have unfavourable levels of risk factors. Accounting for missing data by multiple imputation did not alter our conclusions (online Table DS2). Similarly, excluding dementia-related deaths occurring within 5 years of follow-up, to explore reverse causality in the case of current occupational social class, did not affect our results (online Table DS3).

Discussion

The purposes of the current study were to show that an individual participant meta-analysis technique can be applied to a socio-economic risk factor and also to investigate the association between socioeconomic status and dementia-related death. In order to achieve the former we used a convenience sample of 11 large UK population-based cohort studies. With regard to the latter, the main finding of this study was that educational attainment was associated with dementia death in women but not in men. In men, we also found that, relative to the highest two classes, belonging to the lowest two occupational social classes was associated with an elevated risk of dementia death; a relationship that did not reach statistical significance at conventional levels. There was no association between occupational social class and dementia death in women.

Strengths and limitations

To our knowledge, this study is the first to use an individual participant meta-analysis methodology to examine the association between socioeconomic variables and dementia. In contrast to previous literature-based analyses, an individual participant meta-analysis has the advantage of providing precise estimates of risk marker–disease relationships, reliable information on the shape of a given risk factor–disease relationship (for example dose–response *v.* threshold) and a consistent approach to statistical control for plausible covariates and subgroup analyses. We used a large, well-characterised sample that is representative of the general population in England. This provided sufficient power to allow gender-specific analyses and allowed us to explore the role of a series of explanatory factors. By including two measures of socioeconomic status at different time points we offer some insights into the influence of life-course socioeconomic status on dementia risk.

This notwithstanding, the data have their limitations. Despite the large sample and over 12 000 deaths during follow-up, there were only 622 dementia-related deaths. This is due to the wide age range of individuals included in the survey at baseline – adults aged 35 and over. Although this wide age range increases the generalisability of the findings, it has resulted in a relatively small proportion of individuals dying with dementia and consequently wide confidence intervals, limiting the conclusions that can be drawn. The identified gender differentials should be viewed in the light of this question of power. The number of dementia-related deaths in this study is likely to have been additionally affected by the unavoidable problems of underdiagnosis of dementia in the community,[23] underrecording of dementia on death certificates[24] and diagnoses being inaccurately coded. Non-recording of dementia on death certificates has been highlighted as an important issue, but this seems to be improving. A recent study identified that 71.5% of a clinic sample diagnosed with probable Alzheimer's disease had dementia correctly

recorded on their death certificate.[25] There was no association in that sample between correct dementia certification and area deprivation or premorbid IQ estimated by the National Adult Reading Test (unpublished results available from the author on request), suggesting that individuals reported as having dementia on their death certificate are representative of the population of people with diagnosed dementia in the community, at least in terms of intelligence and level of deprivation.

Comparison with previous studies

Dementia was estimated to affect over 24 million people globally in 2001 and this is expected to rise to over 80 million by 2040.[26] In England and Wales the prevalence of dementia is estimated to vary from approximately 1.5% at age 65–69 to approximately 25.3% over the age of 84.[27] Dementia incidence ranges from 7.4 (95% CI 3.6–16.1) per 1000 person-years at age 65–69 to 84.9 (95% CI 63.0–107.8) per 1000 person-years over the age of 84.[28] However, existing prospective studies of socioeconomic factors have generally been small in scale – only one analysis reported a combined sample larger than 10 000[19] – and few studies measure socioeconomic status at more than one time point.[8] On a related note, the association between education and dementia risk has been reported to be present in women but not in men;[19] it is therefore important that studies are sufficiently large to allow gender-specific analyses. In addition, for older participants – who are most likely to have died with dementia during follow-up – the social class may have been allocated to females on the basis of their husband's occupation, further muddying the waters.

Factors across the lifespan have been implicated in the aetiology of dementia. A series of studies confirm a link between early life socioeconomic status and dementia risk with early parental death – and, potentially, consequent socioeconomic hardship – being highlighted as an important risk factor.[29]

A total of 51 of 88 studies included in a systematic review[6] reported a significant association between a basic education and dementia risk, the remainder reporting no effect. However, only two previous studies report gender-specific effects, showing an effect of education on dementia risk in women but not in men, as found in the current study.

In England, the Education Act 1918 raised the school leaving age from 12 to 14. It was further increased to 15 in 1947 and to 16 in 1973. Participants in the Health Survey for England came from all these educational eras and overall approximately half of men and women stayed on after completion of the compulsory period of education. However, individuals were much more likely to remain in education longer if they were born later: 86.7% of women and 87.2% of men born after 1956 (who therefore had to remain in school until 16) compared with 17.8% of women and 18.5% of men born before 1906 and who could therefore leave school at 12. However, the reference category used, of individuals who remained in full-time education up to 16 years or later, exactly matches those who remained in education after the compulsory school leaving age.

Since children scoring higher on IQ tests, as well as children from a higher occupational social class, are more likely to be given the opportunity to remain in education for longer, a number of studies have investigated the association between childhood mental ability and dementia. A Scottish study identified 50 participants in the 1932 Scottish Mental Survey who had developed dementia and ascertained that their scores on the Moray House Test in 1932 had been significantly lower than their peers in the same area who did not develop dementia.[30] However, a larger subsequent study confirmed that this was the case for vascular dementia but not for Alzheimer's disease.[31] On the other hand, the Nun study identified that low linguistic ability at a mean age of 22 was associated with Alzheimer's disease in the 14 study participants aged 79–96 whose brains were neuropathologically examined post-mortem.[32]

Occupation in adulthood has also been shown to be associated with dementia risk – high 'occupational attainment' is associated with lower dementia risk.[33] However, since the pathology of Alzheimer's disease and probably vascular dementia develops over a very long period of time[34] risk factors must be measured sufficiently early in life for them to have an effect, and exposures immediately before retirement may have little or no effect on dementia risk.

Few studies measure socioeconomic status across the whole lifespan. One study to do so identified early parental death, manual work and physical illness in the spouse or serious illness in a child, both after the age of 65, to be independent risk factors for dementia.[8] However, many of the socioeconomic factors measured in studies are closely linked and disentangling their individual effects can be extremely difficult.

Mechanisms of effect

The role of education and mental ability as potential risk factors for dementia has been linked to the hypothesis of cognitive reserve – that certain individuals' brains are structurally or functionally more resilient to disease or injury. This sprang from the observation that there was no clear relationship between the extent of brain pathology and the clinical manifestations of dementia in an individual. Cognitive reserve might relate to a person's intrinsic make up or could result from external experience, i.e. education and occupation. Indeed, there is evidence that occupation is associated with differences in parietal blood flow in Alzheimer's disease that could be a marker of reserve.[35]

Criticisms of the cognitive reserve hypothesis include the suggestion that the effect merely reflects performance on cognitive tests[36] or that the effect is mediated by lifestyle factors and cerebrovascular risk.[37] The present study used clinical diagnoses of dementia recorded on death certificates and two measures of socioeconomic status at different stages of life. This allows us to demonstrate that the observed association between education and dementia in women was not mediated by adult occupation.

Since an individual with more cognitive reserve would have more advanced pathological changes at the time of diagnosis, it has been suggested that this could be linked with a swifter decline and poorer survival. Some studies have found that individuals with Alzheimer's disease and higher educational and occupational attainment declined faster in their performance on cognitive tests.[38] This aspect of the cognitive reserve hypothesis was not examined by the current study.

Implications

An association between lower educational attainment and dementia in women but not men has a number of implications. First, the mechanism of this association, currently hypothesised to relate to cognitive reserve, must be clarified. Second, the reason that the association is observed only in women should be investigated. It may be that fewer women entered further education and that those who did had to be very intelligent to do so. Thus, length of education in these cohorts could be confounded by intelligence in women to a greater extent than men. However, the identified gender difference may also potentially hold the clue to an intervention to decrease the risk

of dementia in women, if a modifiable risk (or protective) factor could be identified. Lastly, if this association were to reflect a causative link between education and dementia risk, promoting higher and further education, especially for women, could have important public health consequences for a common and serious condition.

In conclusion, this large prospective study shows an association between leaving full-time education at a younger age and dementia death in women, but not in men. This relationship remained after adjustment for alcohol, smoking, cardiovascular disease, diabetes, psychological distress and occupational social class. An association between lower occupational social class and dementia death that did not reach statistical significance at conventional levels was also observed in men, but not in women.

Tom C. Russ, MRCPsych, Alzheimer Scotland Dementia Research Centre, University of Edinburgh; Scottish Dementia Clinical Research Network, NHS Scotland; and Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh; **Emmanuel Stamatakis**, PhD, **Mark Hamer**, PhD, Department of Epidemiology and Public Health, University College London; **John M. Starr**, FRCPEd, Alzheimer Scotland Dementia Research Centre, University of Edinburgh; Scottish Dementia Clinical Research Network, NHS Scotland; and Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh; **Mika Kivimäki**, PhD, Department of Epidemiology and Public Health, University College London; **G. David Batty**, PhD, Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh; and Department of Epidemiology and Public Health, University College London, UK

Correspondence: Tom C. Russ, Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. Email: tom.russ@nhs.net

First received 14 Aug 2012, final revision 18 Feb 2013, accepted 19 Feb 2013

Funding

This work was supported by Alzheimer Scotland. T.C.R. is supported by Alzheimer Scotland and is employed in the National Health Service by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). T.C.R. and J.M.S. are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. T.C.R., J.M.S. and G.D.B. are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council and Medical Research Council is gratefully acknowledged. E.S. is supported by a National Institute for Health Research Career Development Fellowship. M.K. is supported by the Medical Research Council, UK, the US National Institutes of Health (R01HL036310; R01AG034454), the Academy of Finland, Finland, and by a professorial fellowship from the Economic and Social Research Council, UK. G.D.B. was a Wellcome Trust Fellow during the preparation of this manuscript.

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Supplementary Table 1: Survey participants included and excluded from fully-adjusted model examining the association between educational attainment and dementia death: the Health Survey for England 1994-2004

Table DS1 Survey participants included and excluded from fully adjusted model examining the association between educational attainment and dementia death: the Health Survey for England 1994–2004

	Included	Excluded	*P*
Women			
n	31 343	16 040	
Age, years: mean (s.d.)	55.8 (14.5)	57.7 (15.3)	<0.001
Occupational social class I–IIINM, %	62.4	62.4	1.0
Left school <16 years,[a] %	52.5	53.0	0.33
Current smoker, %	22.6	21.1	0.003
Drinks more than recommended alcohol limit,[b] %	14.7	6.4	<0.001
Cardiovascular disease,[c] %	3.8	4.5	<0.001
Diabetes, %	2.7	3.6	<0.001
General Health Questionnaire (GHQ-12) score, mean (s.d.)	1.7 (2.8)	1.5 (2.7)	<0.001
Men			
n	26 790	12 335	
Age, years: mean (s.d.)	55.4 (13.8)	56.1 (14.0)	<0.001
Occupational social class I–IIINM, %	49.3	48.9	0.50
Left school <16 years,[a] %	52.7	55.9	<0.001
Current smoker, %	23.1	23.0	0.79
Drinks more than recommended alcohol limit,[b] %	27.7	13.7	<0.001
Cardiovascular disease,[c] %	5.7	5.7	0.83
Diabetes, %	3.9	5.3	<0.001
General Health Questionnaire (GHQ-12) score, mean (s.d.)	1.3 (2.5)	1.2 (2.4)	<0.001

I–IIINM, professional (I), intermediate (II) and skilled non-manual (IIINM).
a. This corresponds with completing only compulsory schooling.
b. Including angina, myocardial infarction and haemorrhagic or thrombotic stroke.
c. Calculated using gender-specific safe limits: ⩽14 units per week for women and ⩽21 units for men.

Supplementary Table 2: Sensitivity analysis—fully adjusted hazard ratios (95% confidence interval) for the association between occupational social class and educational attainment with dementia death with and without multiple imputation: the Health Survey for England 1994-2004

Table DS2 Fully adjusted hazard ratios (HRs) with 95% confidence intervals for the association between occupational social class and educational attainment with dementia death with and without multiple imputation: the Health Survey for England 1994–2004

	Occupational social class						Age on leaving full-time education					
	Dementia deaths	*n*	HR I–II	HR (95% CI) IIINM	HR (95% CI) IIIM	HR (95% CI) IV–V	Dementia deaths	*n*	HR ⩾16	HR (95% CI) 15	HR (95% CI) ⩽14
Women (fully adjusted model)											
Meta-analysis	264	31 343	1 (ref)	0.88 (0.59–1.31)	0.61 (0.36–1.06)	0.92 (0.62–1.36)	264	31 343	1 (ref)	1.64 (1.02–2.65)	1.76 (1.23–2.53)
Multiple imputation	336	33 556	1 (ref)	0.94 (0.64–1.36)	0.77 (0.47–1.28)	1.07 (0.72–1.58)	336	33 556	1 (ref)	1.52 (0.85–2.71)	1.50 (1.08–2.06)
Men (fully adjusted model)											
Meta-analysis	155	26 790	1 (ref)	1.03 (0.53–2.00)	1.03 (0.63–1.69)	1.33 (0.80–2.21)	155	26 790	1 (ref)	0.98 (0.51–1.89)	1.20 (0.77–1.87)
Multiple imputation	171	27 645	1 (ref)	1.03 (0.56–1.91)	0.98 (0.58–1.68)	1.13 (0.63–2.01)	171	27 645	1 (ref)	0.98 (0.52–1.86)	1.17 (0.76–1.79)

I–II, professional and intermediate; IIINM, skilled non-manual; IIIM, skilled manual; IV–V, part skilled and unskilled.

Supplementary Table 3: Sub-group analysis—excluding deaths within five years of follow up: the Health Survey for England 1994-2004

Table DS3 Subgroup analysis by occupational social class – excluding deaths within 5 years of follow-up: the Health Survey for England 1994–2004

	Dementia deaths	*n*	Hazard ratio (95% CI)			
			I–II	IIINM	IIIM	IV–V
Women (age-adjusted model)						
All data	358	45 487	1 (ref)	1.05 (0.75–1.48)	0.96 (0.63–1.47)	1.33 (0.97–1.83)
Excluding deaths within 5 years	269	45 487	1 (ref)	0.90 (0.58–1.39)	0.85 (0.52–1.39)	1.29 (0.91–1.84)
Men (age-adjusted model)						
All data	210	36 880	1(ref)	1.13 (0.66–1.94)	1.29 (0.89–1.89)	1.52 (1.01–2.29)
Excluding deaths within 5 years	128	36 880	1(ref)	1.15 (0.54–2.44)	1.22 (0.77–1.94)	2.03 (1.23–3.35)

I–II, professional and intermediate; IIINM, skilled non-manual; IIIM, skilled manual; IV–V, part skilled and unskilled.

Appendix B

Other Publications 2010-14

Articles

Russ TC (In press) Hangover Square by Patrick Hamilton (Mindreadings). *Advances in Psychiatric Treatment.*

Feinkohl I, Kellera M, Robertson CM, Morling JR, Williamson RM, Neec LD, McLachlan S, Sattard N, Welsh P, Reynolds RM, **Russ TC**, Deary IJ, Strachan MWJ, Price JF on behalf of the Edinburgh Type 2 Diabetes Study Investigators (2013) Clinical and subclinical macrovascular disease as predictors of cognitive decline in older patients with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetes Care* **36**: 2779-86.

Russ TC, Calvert L & Morling JR (2013) Attitudes to Shared Care for Patients with Dementia: A survey of general practitioners in Edinburgh. *Dementia* **12**: 606-18.

Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, Middleton L, **Russ TC**, Deary IJ, Campbell H, Wang W, & Rudan I, on behalf of the Global Health Epidemiology Reference Group (2013) Epidemiology of Alzheimer's disease and other forms of dementia in China between 1990 and 2010. *Lancet* **381**: 2016-2023.

Russ TC & Morling JR (2012) Cholinesterase inhibitors for mild cognitive impairment. *Cochrane Database of Systematic Reviews* **9**: CD009132.

Starr JM, **Russ TC**, McGrory S (2012) Cognitive and Behavioural Predictors of Alzheimer Disease Progression. *European Neurological Review* **7**: 103-6.

Russ TC (2011) 'Inside Story: thinking about human relations in older age.' Report on a study day held in Edinburgh on 23rd April 2010. *British Journal of Psychotherapy* **27**: 211-3.

Book chapters

Maciver S & **Russ TC** (2014) A plea to "see into the life of things": Thinking psychoanalytically about later life. In: Kate Cullen, Liz Bondi, Judith Fewell, Eileen Francis, and Molly Ludlam (Eds) *Making Spaces: Putting Psychoanalytic Thinking to Work*. London: Karnac.

Editorials

Russ TC, Shenkin SD, Reynish E, Ryan T, Anderson D & MacLullich AMJ (2012) Dementia in acute hospital inpatients: the role of the geriatrician. *Age and Ageing* **41**: 282-4.

Russ TC & Starr JM (2010) Could early intervention be the key in preventing dementia? *BMJ Clinical Evidence* April 2010.

Book reviews

Russ TC (2011) "Behavioral Neurology of Dementia" by Bruce L. Miller and Bradley F. Boeve. *British Journal of Psychiatry* **199**: 522-3.

Russ TC (2011) "How we Treat the Sick: Neglect and Abuse in Our Health Services" by Michael Mandelstam. *The Psychiatrist* **35**: 479.

Russ TC (2011) Bion Today, edited by Chris Mawson. *Psychoanalytic Psychotherapy* **25**: 295-7.

Russ TC (2011) "Guide to the Psychiatry of Old Age" by David Ames, Edmond Chiu, James Lindesay, and Kenneth Shulman. *The Psychiatrist* **35**: 160.

Appendix C

Bayesian disease mapping manuscript (submitted)

Environmental factors explain non-random geographical variation in dementia

Tom C. Russ,[1-3 *] Margaret Gatz,[4,5] Nancy L. Pedersen,[4,5] Jean Hannah,[6]
Grant Wyper,[7] G. David Batty,[3,8] Ian J. Deary,[1,3] John M. Starr[1-3]

[1] Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK.

[2] Scottish Dementia Clinical Research Network, NHS Scotland, UK.

[3] Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh, UK.

[4] Department of Psychology, University of Southern California, Los Angeles, USA.

[5] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

[6] Greater Glasgow & Clyde Nursing Homes Medical Practice, NHS Greater Glasgow & Clyde, UK.

[7] Electronic Data Research and Innovation Service, Information Services Division, NHS National Services Scotland, UK.

[8] Department of Epidemiology and Public Health, University College, London, UK.

*Correspondence to: Dr Tom C. Russ, Alzheimer Scotland Dementia Research Centre, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK.
Telephone: +44 (0)131 650 4341; Fax: +44 (0)131 242 6370; Email: tom.russ@nhs.net

Abstract: In the absence of successful treatment modalities, there is a need to understand dementia aetiology in order to delay or prevent its onset. One route to identify potentially modifiable risk factors is examining geographical variation in dementia rates. We present two complementary Bayesian disease mapping studies: a twin study in Sweden and a study in Scotland with individuals located in early and mid-life. Both studies show variation in dementia rates of two- to three-fold. These analyses are the first to separate genetic and environmental influences on geographical variation in dementia rates and identify that this variation is likely to be the result of unshared environmental factors which have the majority of their effect in adolescence and adulthood.

One Sentence Summary: Dementia risk varies with geography – the risk in the highest areas is approximately double that in the low risk areas – and it is environmental factors which drive this effect.

Word count: 2882

None of the material in this submission has been published anywhere else, including the internet, but preliminary findings were presented at AAIC 2013 in Boston, July 2013.

Dementia comprises a group of progressive neurodegenerative and cerebrovascular disorders affecting approximately one in twenty adults over the age of 60 years worldwide(*1*). It is characterised by impairments in several domains of cognition, prominently memory, in addition to deterioration in day-to-day functioning. Despite numerous drug trials, there are no disease-modifying treatments and therefore there is an urgent need to understand the aetiology of dementia in order to attempt to delay or prevent its onset. Whereas there is a familial aspect of dementia risk,(*2*) the importance of non-genetic factors is clear(*3, 4*) and these may act at different points throughout the life course.(*5*) Thus, interventions to delay or prevent dementia by modifying these risk or protective factors may have to begin in midlife or even earlier.

Studying the geography of diseases and noting which factors might affect their distribution is a powerful hypothesis-generating methodology. Findings can then be used to investigate aetiology. The geographical distribution of cases of dementia is not random(*6*) and is likely to result from both genetic and environmental effects.(*7*) However, in order to be more informative about putative risk or protective factors, studies must be conducted on small areas – variation in the exposure of interest may be masked by covering too large an area. Such studies are scarce, however, and none have adequately investigated the relative contribution of genetic and environmental factors to the distribution of dementia.(*6*) Here, we present two complementary disease-mapping studies using data from Sweden (pooling data from four twin studies) and Scotland (cohort study) to test several linked research questions: first, is there non-random variation in dementia in these countries?; second, in the twin study, is this variation completely explained by familial and genetic factors or are environmental factors important?; and third, in the cohort study, do different risk or protective factors have their effects at different stages of life? To our knowledge, this is the first study to attempt to separate genetic and environmental effects on geographical variation in dementia in this way and the first to examine geographical variation at two points in time.

Non-random variation of dementia in Swedish twins

We pooled four Swedish twin studies to give a total sample of 10,683 men and 13,949 women (mean±SD age 78.2±8.2 and 80.2±8.1 years, respectively). A total of 343 male and 650 female dementia cases were identified. Table 1 shows summary statistics from age-adjusted Bayesian disease mapping models of the male and female Swedish twins. These hierarchical conditional logistic regression models showed substantial variation in dementia risk by area in men and women with an increased age-adjusted odds in the north compared to the south (Fig. 1). The figure shows area-level effects – individual- and twin-level random effects have been removed. Thus, this variation is likely to result from non-shared environmental factors because familial and genetic factors will have been largely removed with the twin-level random effects. Almost two-thirds of the variance of the area effect is spatially structured, as opposed to non-spatially structured error. Models using Alzheimer dementia as the outcome showed similar effects (Fig. S1).

There were no differences in the twin random effects – which give some indication of between-pair variation in dementia odds – between monozygotic and dizygotic twins in men or women (t=-0.51, P=0.61 and t=-0.05, P=0.96 respectively) further suggesting that genetic factors are not driving the distribution of dementia observed in this study. Furthermore, the age-structure and geographical distribution of the twins was similar to that of the general population (Kolmogorov-Smirnov test: men D=0.1217, P=0.1217; women D=0.0952, P=0.3581) suggesting that the observed findings were not the result of an excess of elderly twins in the north of Sweden.

To test formally whether genetic factors explained non-random geographical variation, we performed a subgroup analysis including only monozygotic twins that were discordant for dementia (i.e. cases and controls were exactly matched by age, sex and genetically) with regard to the quartile of dementia risk of the area where they were resident (Table 2). We tested whether the proportion of twins with dementia differed between the highest and lowest quartiles. We found there was a two- to three-fold risk ratio between the lowest and highest quartiles (Men $\chi^2(3)=14.9$, $p = 0.002$; Women:

$\chi^2(3)=22.2$, $p < 0.001$) representing environmental factors, similar to the overall effect size of non-random geographical variation observed in the entire sample.

Changes in non-random variation of dementia over the life course

In the second study investigators traced participants in the 1932 Scottish Mental Survey (SMS1932) in which a validated IQ-type test was administered to almost all children attending schools in Scotland and born in 1921 (n=87,498)(*8*). Dementia status was ascertained through record linkage to hospital discharge and mortality registers. A total of 19272 men (44.3% overall) and 18325 women (42.6% overall) were traced. County of schooling was recorded for all participants. Postcode sector of residence at the time of first admission to hospital in mid-life was missing or erroneous for 7854 individuals, leaving an analytic sample for the mid-life models of 14,864 men and 14,879 women. Age 11 IQ data were additionally missing for 804 men and 855 women. Over approximately 80 years of follow up, 13,317 male and 13,423 female deaths were recorded, leaving 10.4% of men and 9.8% of women alive. A total of 1307 male and 2298 female dementia cases were identified, through hospital discharge records, death certification, or primary care records.

The SMS1932 models using county of schooling aged 11 years show very little geographical variation in dementia odds in men or women (Table 1, Fig. 2). On the other hand, the models using mid-life location show substantial variation in dementia odds in both sexes. Setting aside data from the islands which are more difficult to model, the Scottish data mirrored those of Sweden with generally low risk in the south of the country increasing further north (Table 1, Fig. 2). Alzheimer dementia models using mid-life location gave similar results (Fig. S1).

Sensitivity analyses

In order to demonstrate that the observed distribution of dementia cases was not the result of artefact, we examined a number of possible alternative explanations. Since not all original SMS1932 participants were traced, geographical variation in ascertainment rates alone could explain the non-random pattern observed. The linkage rate varied

across the country (Table S1 and Fig. S2) and in only six counties for men and five for women (out of 34) were the linkage rates more than 50%. However levels of ascertainment did not mirror the dementia odds and it is unlikely that ascertainment alone could explain the substantial variation observed, particularly in the mid-life models (i.e. maximum to minimum county ascertainment rate ratios were 1.80 for men and 1.56 for women compared to dementia rates varying by over three times, Fig. 2).

Lower intelligence has been shown to be associated with an increased risk of dementia,(*9*) though perhaps more strongly with vascular dementia than Alzheimer disease(*10*). It is possible that either bias in record linkage related to intelligence or geographical variation in baseline intelligence might explain the observed variation in dementia odds. Whereas baseline intelligence (IQ based on total score) was higher in individuals who were untraced than those identified through record linkage (linked: mean±SD 99.7±14.9; untraced: 100.2±15.1; P<0.001), the level of significance is likely to result from the large sample size and a difference of 0.03 standard deviations is unlikely to be important. There was some variation in the mean intelligence of individuals who were and were not successfully identified by record linkage by county of schooling aged 11 years (Table S1), but the difference was only statistically significant at conventional levels in five counties (Aberdeenshire, Ayr, Dunbarton, Edinburgh, and Selkirk) and the largest difference was 3.3 IQ points or 0.2 standard deviations. This variation, given the known effect size of IQ on dementia risk,(*9*) is unlikely to have given rise to the substantial variation in dementia observed in the present study. Similarly, there was not sufficient variation in baseline intelligence to explain the observed variation in dementia rates (Fig. S3).

We next examined the possibility that our findings could relate to under-ascertainment of dementia cases. Compared to all sources of case-identification, death certification alone missed 233 male cases of dementia (17.8%) and 375 (16.3%) in women (Table S2) – better than the 28.5% non-reporting of dementia previously described in a Scottish study.(*11*) Examining SMS1932 participants who were registered with the Greater Glasgow & Clyde Nursing Homes Medical Practice showed us that 4/12 men (33.3%) and 13/27 women (48.1%) with dementia were missed but that primary care had no

record of a dementia diagnosis in 4/8 men (50%) and 3/14 women (21.4%) identified as having dementia through record linkage (Table S3). Thus the present methodology did not identify all cases of dementia, but primary care records (which would most likely be the next source of data consulted) similarly did not identify every case already found by record linkage. In order to examine geographical bias of ascertainment by record linkage in more detail we calculated the proportion of extra cases of dementia which would be identified by using prescriptions for dementia drugs over and above those identified using the record linkage methodology in the present study. Figure S4 shows that the underascertaiment of dementia identified in this way does vary across the country, but that this pattern alone is very unlikely to have resulted in the findings of the present study, indeed in the areas with highest dementia odds, it is likely that we under-ascertained the number of cases of dementia more than in the rest of the country, particularly in men.

Discussion

Our main findings are substantial non-random geographical variation in dementia rates in two countries; the general pattern was of higher rates in the north compared to the south. This variation is not completely explained by familial or genetic factors, confirming the importance of other environmental factors in dementia, and there was a doubling of risk between the lowest and highest risk areas shown both in the 90% quantile ratios of the main models and in the subgroup analysis of monozygotic Swedish twins. The Scottish data suggest that these environmental factors may have the majority of their effect in adolescence and adulthood.

An increased risk of dementia in northern areas has previously been described in Finland(*12, 13*) and China.(*14*) However, to our knowledge, this is the first study to attempt to separate genetic and environmental effects on geographical variation in dementia in this way. A study in Newfoundland which identified a difference in dementia risk in those born on the north side of Bonavista bay compared to the south suggested that genetic relatedness might account for a proportion of the effect by examining the number of surnames in each group.(*15*) A Scottish study of young-onset Alzheimer disease examined the number of common ancestors in order to estimate case

kinship and concluded that familial factors partly contributed to the high incidence of dementia in Lanarkshire.(*7*) A recent systematic review of geographical variation in dementia based on within-study comparisons did not identify any further studies attempting to separate genetic and environmental contributions.(*6*)

Both of the present studies have limitations but their respective methodologies are complementary and we can be reassured by the fact that both studies give similar results. Less than half of the SMS1932 cohort was traced via record linkage. It is likely that a number of factors related to whether or not an individual was traced, including: women changing their name on marriage (though the national records endeavour to record maiden name); emigration or death prior to the beginning of the records (1981 for mortality records), including World War II; and the probabilistic linkage methods used may have meant that common names could be associated with a large number of potential links and therefore the linkage 'score' would fall below the acceptable threshold, i.e. when it is uncertain whether two sets of records belong to the same person. However in the Swedish twins study – at least in HARMONY which constituted the vast majority of the sample – dementia ascertainment approached completeness.(*16*) The Swedish twins study includes individuals of a variety of ages which introduces heterogeneity and is likely to mask any cohort effects. On the other hand, the SMS1932 study is a narrow age cohort. Furthermore the Swedish twins study only has the most recent location available whereas the SMS1932 study has location available at two points in life offering some insights into life course effects. Indeed, 94.2% of a sample of 854 SMS1932 participants (approximately 1% of the cohort) whose birth records were examined attended school in the county of their birth or a neighbouring county. The use of adjacency matrices recording neighbouring areas in the Bayesian disease mapping models means that it is likely that, for the majority of the sample, almost all exposures between birth and age 11 will have been captured. However, these adjacency matrices make the results for islands more difficult to interpret since they have very few automatic neighbours.

Finally, the SMS1932 study does not include information on the genetic relatedness between participants but in the Swedish twins study this information is completely

known and can be included in the models. A rough comparison of genetic risk in the SMS1932 study can be carried out using *APOE* e4 status in the Aberdeen and Lothian Birth Cohort 1921 studies(*17, 18*) – subsamples of the SMS1932 cohort – which are carried out in areas of Scotland shown in the current study to be at high risk and average risk, respectively. The prevalence of one or more *APOE* e4 alleles in the ABC 1921 study was 24.3%(*19*) and in the LBC 1921 study was 26.0%(*20, 21*).

Following the finding that non-random variation in dementia prevalence is unlikely to be fully explained by genetic effects, further corroboration could be sought by accessing biobank data to create polygenic risk scores across various regions in these two countries. Researchers will then need to identify potential risk or protective factors and ascertain whether modifying these factors could alter an individual's risk of developing dementia, raising the possibility that dementia could become a preventable disease.

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Acknowledgments: TCR was supported by Alzheimer Scotland during the preparation of this manuscript and employed in the UK National Health Service by the Scottish Dementia Clinical Research Network, which is funded by the Chief Scientist Office (part of the Scottish Government Health Directorates). He is now employed by NHS Education for Scotland and NHS Lothian. TCR and JMS are members of the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland. TCR, JMS and GDB are members of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/ 84698). Funding from the BBSRC, EPSRC, ESRC, and MRC is gratefully acknowledged.

TCR would like to thank Dr William Mackaness for guidance on GIS, Professor Nicky Best and Dr Léa Fortunato for advice on modelling, Dr Janet Murray and the Privacy Advisory Committee for approving the record linkage, and Andy Duffy for carrying it out.

JMS conceived and designed the study. TCR, MG, NLP, JH, GW, and IJD were responsible for acquisition of the data. TCR and JMS were responsible for analysis and interpretation of the data. TCR drafted the manuscript and all authors critically revised the manuscript for important intellectual content. TCR did the statistical analysis. JMS obtained funding. JMS was responsible for study supervision. TCR and JMS are the study guarantors.

Conflicts of interest: None.

Table 1. Results from Bayesian disease mapping models

	SWEDEN	SCOTLAND	
		Childhood location	Mid-life location
MEN			
Total N	10,683	19,272	14,864
Dementia cases	343	1307	1244
QR90[1] (95% CI)	1.49 (1.08, 3.11)	1.17 (1.07, 1.37)	2.48 (1.73, 3.47)
$Frac_{spatial}$[2], % (95% CI)	66 (4, 99)	42 (3, 90)	96 (78, 100)
OR per standard deviation increase in age (95% CI)	-[3]	2.10 (1.98, 2.23)	2.04 (1.90, 2.18)
WOMEN			
Total N	13,949	18,325	14,879
Dementia cases	650	2298	2207
QR90[1] (95% CI)	2.15 (1.10, 6.08)	1.20 (1.07, 1.49)	4.07 (3.07, 5.45)
$Frac_{spatial}$[2], % (95% CI)	59 (1, 100)	38 (3, 92)	75 (40, 100)
OR per standard deviation increase in age (95% CI)	-[3]	2.44 (2.31, 2.58)	2.37 (2.22, 2.52)

[1] QR90 = 90% quantile ratio comparing the odds of dementia in the areas on the 5th and 95th centiles

[2] $Frac_{spatial}$ = the fraction of the variance of the area effect which is spatially structured

[3] Since age-adjustment was adjustment for age at diagnosis of dementia for cases and age at death for controls, it is not possible to compute meaningful odds ratios for increasing age

Table 2. Individuals from complete monozygotic Swedish twin pairs discordant for dementia allocated to quartiles of dementia odds, according to area of residence

		Dementia odds ratio			
		Q1 (low)	Q2	Q3	Q4 (high)
MEN					
No dementia	N	19	16	14	18
	(%)	(76.0)	(66.7)	(41.2)	(35.3)
Dementia	N	6	8	20	33
	(%)	(24.0)	(33.3)	(58.8)	(64.7)
WOMEN					
No dementia	N	35	19	18	28
	(%)	(74.5)	(61.3)	(31.0)	(43.8)
Dementia	N	12	12	40	36
	(%)	(25.5)	(38.7)	(69.0)	(56.3)

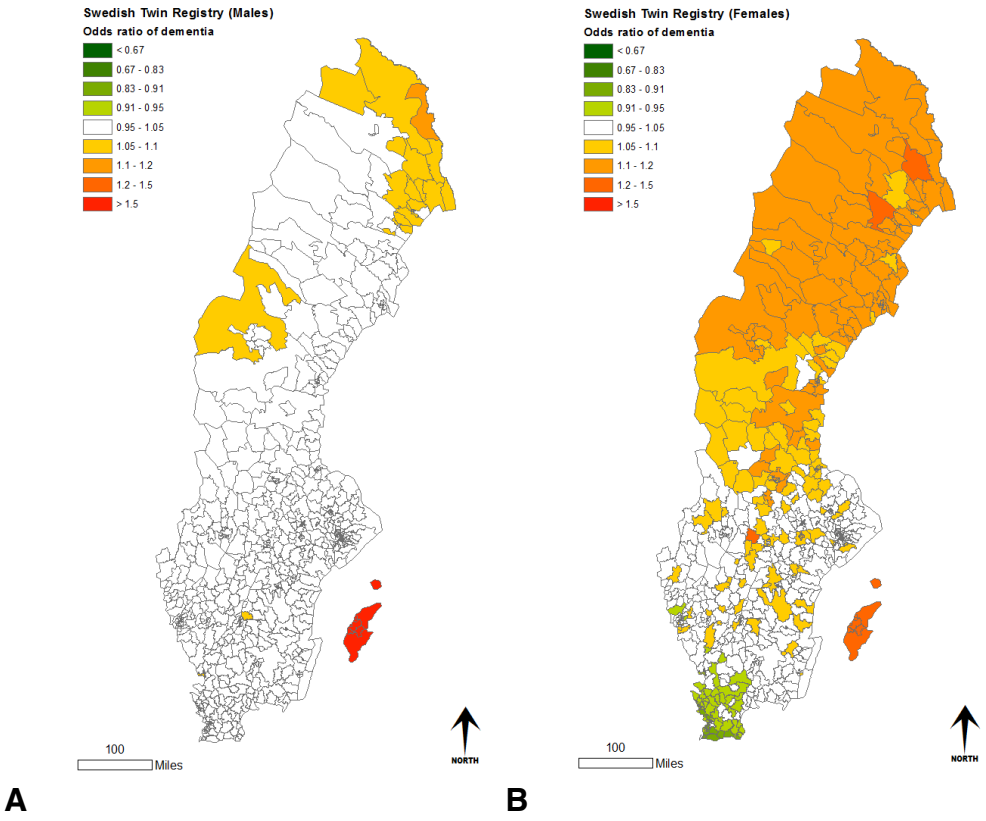

Fig. 1. Odds ratio of dementia in male (A) and female (B) Swedish twins with twin random effects and individual-level effects (age) removed

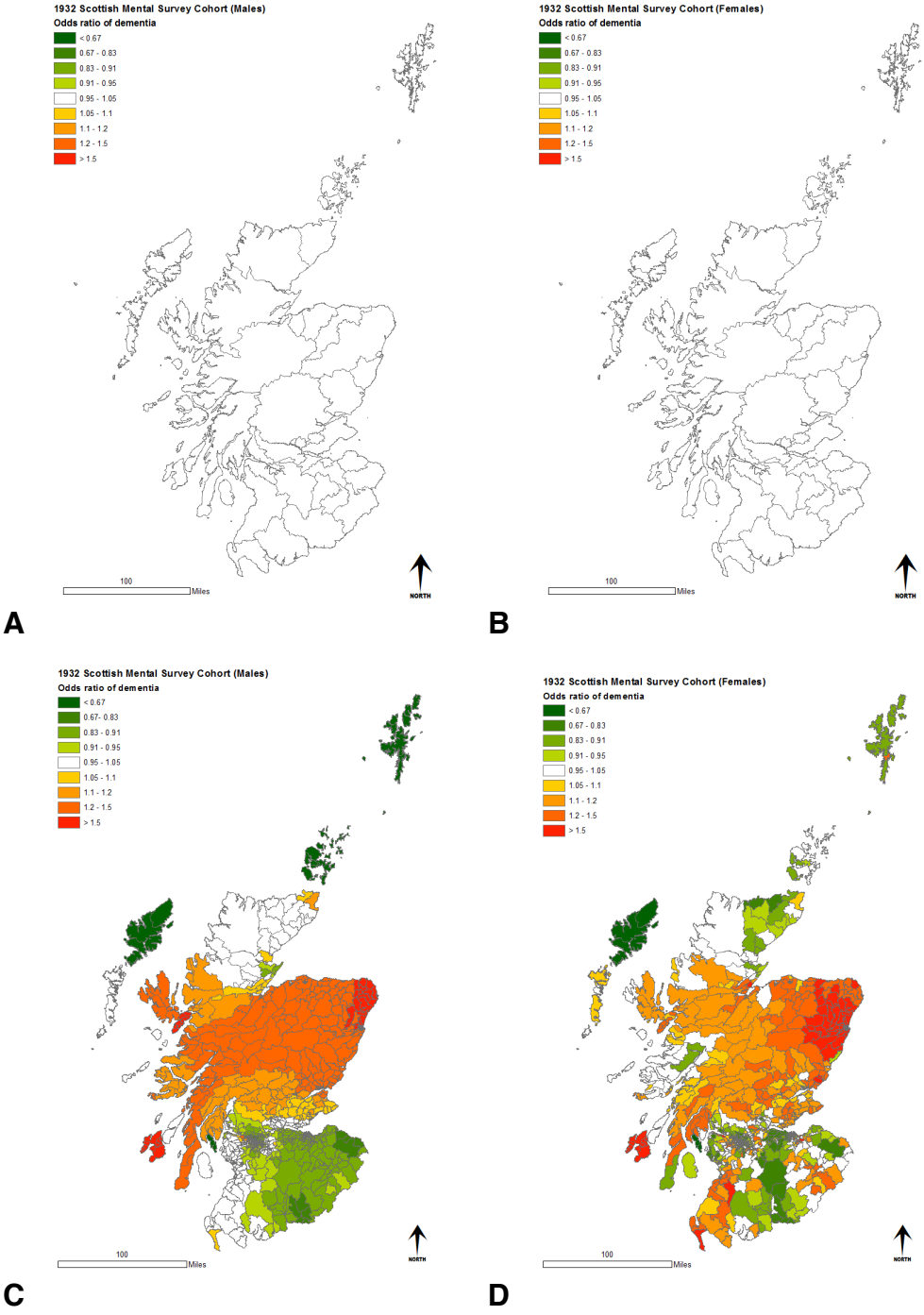

Fig. 2. Odds ratio of dementia in the SMS1932 cohort by age 11 location (men A; women B) and mid-life location (men C; women D) with individual-level effects (age) removed from all models

Supplementary Materials:

Materials and Methods

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Tables S1-S3

Figures S1-S5

Materials and Methods

Data: Swedish study

Participants were included from four related studies: the Study of Dementia in Swedish Twins (HARMONY);(*22*) the Swedish Adoption/Twin Study of Aging (SATSA);(*23*) Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-twin);(*24*) and Gender and Health: A Study of Older Unlike-Sex Twins (GENDER)(*25*). HARMONY was a cross-sectional study but the rest are longitudinal in design. The majority of the sample came from HARMONY (83.6%; SATSA 11.6%; OCTO-Twin 2.8%; GENDER 2.0%; twins who participated in HARMONY and another study were recorded as being included in the former for the purposes of this study).

Details of the methodology of these studies is described in detail in the cited articles but, briefly, HARMONY involved telephone screening of all twins born before 1959, irrespective of co-twin vital status (though twins born before 1926, in the first wave of the Swedish Twin Registry, were only registered if both twins were alive and responded at the time of compilation of the registry). All individuals screening positive – and their co-twin, if still living – were requested to attend for a clinical assessment, in addition to a sample of normal control twin pairs. SATSA included same-sex twin pairs from the Swedish Twin Registry who reported that they had been reared apart, were born in 1935 or earlier, and at least one of whom was alive in 1987 and matched control twin pairs who had been reared together. Dementia status was identified by in-person cognitive testing in a sub-sample, telephone screening, linkage with a psychiatric registry, and follow-up every three years for participants not diagnosed with dementia. OCTO-twin included twins aged 80 years and older who were alive in the period 1991-3. They participated in a comprehensive cognitive test battery administered by a nurse at their place of residence. GENDER included unlike-sex twins born in the years 1906-25; only same-sex twins had been initially entered onto the Swedish Twin Registry due to the technicalities of the genetic models used at the time. These individuals received questionnaires about health, demographic, and psychosocial topics.

The total sample comprised 27,680 individuals, 24.8% of whom were monozygotic. Dementia status is known for all participants and their location of residence (5-digit zipcode) in 2008 was obtained by linkage to the National Population Registry. This locator was shortened to a 3-digit zipcode, of which areas there are 568 in Sweden. Zipcode data were missing or incorrect for 1504 men and 1544 women. Age was recorded for all individuals – age at diagnosis for cases and age of death or censoring for controls. Thus people with dementia had a lower average age than those without and so it was not possible to calculate odds ratios of dementia risk according to age. All participants gave informed consent and ethical approval was granted by the Ethics Committee of Karolinska Institutet, the USC Institutional Review Board, and the Swedish Data Inspection Board.

Data: Scottish study

On 1st June 1932 almost every child aged 11 at school in Scotland and born in 1921 sat an identical intelligence test, a version of the Moray House Test No. 12 (N=87,498).(*26*) The purpose of this Scottish Mental Survey (SMS1932) was to examine the distribution of intelligence across the whole population. The first name, surname, date of birth, school attended, county, and mental ability score were recorded in a ledger.

In the late 1990s the ledgers for all but three Scottish counties (Angus, Fife and Wigtown; 6309 individuals with mental ability scores recorded, 7.2%) were discovered and subsamples of the initial population studied in Edinburgh (Lothian; N=550) and Aberdeen (N=275) have been followed up in later life to provide insights into, amongst other things, the stability of mental ability over the lifespan.(*27-29*) In contrast, the present study is based on record linkage of the entire SMS1932 cohort for whom data were available (Total N=86,520 including individuals without mental ability scores; N with mental ability scores=81,189 – these data were missing, for example, if the pupil had been recorded as attending the school in 1932 but had been absent on 1st June).

Apart from 73 participants in the Lothian Birth Cohort 1921 study (0.08%) who had explicitly withdrawn consent to data linkage, the Information Services Division of NHS National Services Scotland (ISD) linked data for all SMS1932 participants using probabilistic methods with Scottish Morbidity Records recording every admission to general (SMR 01) and psychiatric hospitals (SMR 04) in Scotland since 1981 and death certificate data held by the General Register Office for Scotland. Both sources of data provide the individual's age and residential location on admission to hospital or death, anonymised to the level of postcode sector, of which there are 953 in Scotland. From the original SMS1932 cohort of 86,520, 37,597 were traced (43.5% overall). Residential location on first mid-life admission to hospital was used as mid-life location for the models.

All diagnoses recorded in SMR or on death certificates were provided which were coded according to the International Classification of Diseases (ICD), 9th(*30*) and 10th(*31*) revisions. Dementia cases were identified by any mention of codes 290.0 to 290.4, 290.8, 290.9, 291.1, 291.2, 294.1, 294.2, 294.8, 294.9, and 331.0 to 331.9 for ICD-9 and codes F00-F05.1, F09, G30, and G31 for ICD-10. In addition, the Greater Glasgow & Clyde Nursing Homes Medical Practice (a primary care medical provider which exclusively treats residents of nursing homes) were approached to provide details of all patients on their list born in 1921 with details of any clinical dementia diagnosis. These data were also linked with the SMS1932 data.

Place of birth was located for a random sample of approximately 1% of the original SMS1932 dataset (N=854) from original birth certificates held by the National Register of Scotland (General Register House, Edinburgh). It was not possible to locate records for 13.1% (N=112) either because there were no birth records with that name and date of birth or there were too many associated with a very common name, such as the surname Smith, to be certain which was this particular SMS1932 participant. Of the 742

for whom birth certificates were located, 154 attended school in a different county to that of their birth, of whom 111 were born in the neighbouring county to the one in which they attended school Thus, 43/742 (5.8%) moved further than to a neighbouring county between birth and age 11 years.

Ethical approval of the Scottish study was granted by South East Scotland Research Ethics Committee 3 and the linkage was approved by NHS Caldicott Guardians, the Privacy Advisory Committee of ISD, and the Community Health Index Advisory Group.

Statistical methods

We used hierarchical Bayesian disease mapping models to produce area-level odds ratios of dementia relative to the average odds in that map with random variation due to small numbers smoothed by shrinking the effect estimate for each region towards the mean of the surrounding areas.(*32-35*) We constructed Bernoulli logistic regression models with two levels: (a) the individual, including adjustment for individual-level covariates; and (b) the area. In order to examine the area effect, we used the Besag-York-Mollie model(*36*) which allows separation of random effects into spatially structured and unstructured parts without making a strong spatial assumption and which is widely used in disease mapping studies.(*37, 38*) In the Swedish analyses, we had an additional level between the individual and the area – the twin pair; we added separate random effects for the monozygotic and dizygotic twins. Syntax for both the Swedish and Scottish models is reproduced below. We used R version 2.15.2 and the R2WinBUGS package(*39*) to run Markov chain Monte Carlo simulations in WinBUGS (the Windows implementation of Bayesian inference Using Gibbs Sampling).(*40-42*) Model convergence was diagnosed using the Brooks-Gelman-Rubin statistic(*43, 44*) and models were compared using the Deviance Information Criterion (DIC), a Bayesian model comparison criterion analogous to the Akaike Information Criterion.(*45*) We extracted area effects (odds ratios with accompanying 95% confidence intervals) computed by exponentiating the sum of the two area random effects for men and women separately – i.e. with individual or individual and twin-level effects removed.

We produced unadjusted models and age adjusted models. In the Swedish twins study, age at diagnosis was used for cases and age at death or censoring for controls. However, in the SMS1932 study, the precise date of diagnosis was not known for cases and so age at death or censoring was used for both cases and controls in this study. In preliminary analyses the change in DIC indicated that adjusting for age substantially improved the models and so the most basic models we report are age-adjusted. We also constructed models using Alzheimer disease as the outcome of interest.

Model results are displayed as maps of odds ratios produced using ArcMap 10 using shapefiles from the Swedish Postal Service (http://www.postnummerservice.se; accessed 10th April 2013) and the UK BORDERS service, now part of the Economic and Social Research Council UK Data Service (http://edina.ac.uk/census/; accessed

10th April 2013). We also report the fraction of the area-level variance which was spatially structured, as opposed to unstructured error. The overall variation in area effect in each model is summarized by the 90% quantile ratio (QR90) which compares the odds ratio of dementia in the areas on the 5th and 95th centiles.

Since the models produce a distribution for each outcome of interest (e.g., odds ratio) it is possible to examine statistical significance by the proportion of the distribution is greater or less than unity. Simulation studies in cancer research have suggested that a cut off of 80% is reasonably sensitive in identifying truly raised or decreased risks, though this rule is less robust when fewer than 20 cases per area are expected.(*46*) We follow this approach in the present study and produce maps showing the posterior probability that the odds ratio for an area is greater than or less than 1 (Fig. S5).

Sensitivity analyses

In addition to the main analyses, we planned a number of sensitivity and supplementary analyses in order to investigate whether our results could be due to a number of factors: (A) the geographical distribution of the sample compared to the general population in the Swedish twins study; (B) environmental factors by examining the subgroup of monozygotic Swedish twins who were discordant for dementia; (C) differential linkage rates in different regions in the SMS1932 study; (D) whether the observed geographical variation could be caused by variation in mental ability – which has been shown to be associated with social class and birth weight in a subsample of the SMS1932 cohort;(*47*) and (E) differential ascertainment of dementia due to the source of diagnoses identified.

First, we wanted to confirm that results from models using the Swedish twins were generalizable to the entire population of Sweden and to confirm that there was no consequent geographical bias. We obtained demographic data on the Swedish population in 2008 from Statistics Sweden (http://www.scb.se/; accessed 10th April 2013). We then compared the Swedish twins over the age of 65 years stratified by county of residence (geocoded from the 5-digit zipcode using ArcMap 10) and 5-year age band to the general population using the Kolmogorov-Smirnov test. There were relatively few twins under the age of 65.

We attempted to confirm a substantial environmental contribution to any observed non-random distribution of cases by a subgroup analysis examining individuals within monozygotic twin pairs discordant for dementia. These groups of men (N=134) and women (N=200) with and without dementia are perfectly matched for age, sex, and genotype since each group contains one member of each monozygotic twin pair. We allocated these individuals to four groups defined by quartiles of the area-effect (odds ratio of dementia) derived from the main disease mapping models and examined the proportion of dementia cases in each group.

In the SMS1932 study we were able to identify from the original dataset (N=86,520) individuals whose records had been traced by ISD and those who were not traced. This

allowed us to examine the possibility of a geographical bias resulting from differential linkage rates in different areas. Thus we compared linkage rates by county of schooling aged 11 years for all survey participants. Additionally we were able to compare mental ability scores for individuals with successful record linkage and those without, both at a national level and by county.

Given the relatively low linkage rates, it was important to estimate under-ascertainment of dementia in the SMS1932 study and we were able to attempt this in two ways: (1) by comparing primary care diagnoses made in the Greater Glasgow & Clyde Nursing Homes Medical Practice to the diagnoses identified by record linkage in the linked dataset; and (2) by identifying cases of dementia through the Prescribing Information System (PIS), a national database for Scotland holding information on prescriptions dispensed in the community, by looking for prescriptions for cholinesterase inhibitors or memantine. The PIS is indexed by each patient's Community Health Index number (a unique 10-digit identifier used in the National Health Service in Scotland). From calendar years 2009 to 2012 the range of yearly CHI capture for dementia prescriptions is 80.7%-87.7% and the overall level of CHI completeness on dementia prescriptions for the time period is 86.0%. We were not permitted to link the analytic dataset to the PIS but we were able to identify all dispensed prescriptions for these drugs to individuals born in 1921, which is likely to be a broadly comparable population, during 2009 to 2012. These prescription data were additionally linked to SMR01, SMR 04, and mortality data using deterministic methods. We then calculated the proportion of cases of dementia identified from any source which were only identified by PIS for each Health Board in Scotland. These data were then mapped with ArcMap 10 using shapefiles also from the UK BORDERS service.

WinBUGS code: Swedish model (age-adjusted)

```
model {
      for(i in 1:NPeople) {
            Y[i] ~ dbern(p[i])
            logit(p[i]) <- alpha + beta.age*AGE[i]
                  + twin.re[TWIN[i]] + V[AREA[i]] + U[AREA[i]]
            }

# TWIN-LEVEL RANDOM EFFECTS
# NTwins = number of twins; NMZ = number of MZ twins
# Random effects for MZ twins
for(j in 1:NMZ) {
      twin.re[j] ~ dnorm(0, prec.mz)
      }
# Random effects for DZ twins
for(k in  (NMZ+1):NTwins) {
      twin.re[k] ~ dnorm(0, prec.dz)
      }

# AREA-LEVEL EFFECTS
# Unstructured effects (V)
for(l in 1:NArea) {
      V[l] ~ dnorm(0, prec.v)
      area.effect[l] <- exp(V[l] + U[l])
      }

# Spatially correlated effects (U)
U[1:NArea] ~ car.normal(adj[], weights[], num[], prec.u)
for(m in 1:sumNumNeigh) {weights[m] <- 1}

# PRIORS
alpha ~ dflat()
beta.age ~ dnorm(0, 0.00001)
prec.mz ~ dgamma(0.5, 0.0005)
prec.dz ~ dgamma(0.5, 0.0005)
prec.v ~ dgamma(0.5, 0.0005)
sigma2.v <- 1/prec.v
prec.u ~ dgamma(0.5, 0.0005)
sigma2.u <- 1/prec.u
sigma2.u.marginal <- sd(U[]) * sd(U[])

# OUTCOME MEASURES
OR.age <- exp(beta.age)
# Fraction of total variation in log odds due to spatial effects
frac.spatial <- sigma2.u.marginal / (sigma2.u.marginal + sigma2.v)
# 90 percent quantile ratio
QR90 <- ranked(area.effect[], N95) / ranked(area.effect[], N5)
}
```

WinBUGS code: Scottish model (age-adjusted)

```
model {
      for(i in 1:NPeople) {
            Y[i] ~ dbern(p[i])
            logit(p[i]) <- alpha + beta.age*AGE[i]
                                  + V[AREA[i]] + U[AREA[i]]
            }

# AREA-LEVEL EFFECTS
# Unstructured effects (V)
for(l in 1:NArea) {
      V[l] ~ dnorm(0, prec.v)
      area.effect[l] <- exp(V[l] + U[l])
      }

# Spatially correlated effects (U)
U[1:NArea] ~ car.normal(adj[], weights[], num[], prec.u)
for(m in 1:sumNumNeigh) {weights[m] <- 1}

# PRIORS
alpha ~ dflat()
beta.age ~ dnorm(0, 0.00001)
prec.v ~ dgamma(0.5, 0.0005)
sigma2.v <- 1/prec.v
prec.u ~ dgamma(0.5, 0.0005)
sigma2.u <- 1/prec.u
sigma2.u.marginal <- sd(U[]) * sd(U[])

# OUTCOME MEASURES
OR.age <- exp(beta.age)
# Fraction of total variation in log odds due to spatial effects
frac.spatial <- sigma2.u.marginal / (sigma2.u.marginal + sigma2.v)
# 90 percent quantile ratio
QR90 <- ranked(area.effect[], N95) / ranked(area.effect[], N5)
}
```

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Table S1. Rates of record linkage in men and women and mean intelligence in linked and untraced participants (both sexes pooled) in the 1932 Scottish Mental Survey Cohort by county of school attended age 11

County	Linkage rate		Linked		Untraced		
	Men	Women	N	mean±SD IQ	N	mean±SD IQ	P
Aberdeen	51.4	47.8	1993	102.2±14.5	1957	101.5±14.3	0.107
Aberdeenshire	50.1	50.1	935	97.2±15.0	957	95.7±15.5	0.030
Argyll	42.1	43.6	495	102.2±16.1	364	101.1±15.9	0.318
Ayr	46.6	47.8	3901	97.5±16.1	3498	96.1±15.8	<0.001
Banff	51.4	47.8	586	99.5±15.4	582	99.3±14.3	0.816
Berwick	39.9	49.8	219	104.8±14.8	183	104.3±15.6	0.767
Bute	31.4	43.6	142	100.3±15.0	83	103.8±15.0	0.091
Caithness	42.9	48.6	254	101.5±16.7	211	101.4±16.7	0.905
Clackmannan	44.3	43.2	348	99.0±15.5	272	98.4±14.7	0.675
Dumfries	40.9	41.1	850	103.2±15.8	596	104.2±14.8	0.207
Dunbarton	40.0	42.0	1657	101.6±14.6	1162	102.7±14.0	0.043
Dundee	44.3	44.6	1675	102.2±14.1	1371	101.8±14.4	0.374
East Lothian	48.7	51.4	398	100.7±15.0	410	99.5±15.4	0.233
Edinburgh	41.2	46.2	3750	102.6±14.5	2961	100.9±14.3	<0.001
Glasgow	39.2	41.3	11276	100.0±15.1	7652	99.8±14.7	0.374
Inverness	43.8	37.3	445	98.5±16.1	301	99.8±16.2	0.293
Kincardine	48.3	50.8	233	99.7±15.4	230	99.4±14.0	0.775
Kinross	46.8	39.6	57	99.7±15.6	41	97.8±14.8	0.532
Kirkcudbright	39.1	45.2	301	100.4±14.5	226	100.7±14.3	0.832
Lanark	39.0	43.0	6560	99.5±14.8	4607	99.3±14.5	0.374
Midlothian	51.3	46.2	863	99.9±15.5	828	98.9±14.4	0.175
Moray	47.0	49.0	393	101.7±13.9	361	101.9±14.4	0.854
Nairn	45.0	35.9	80	100.5±14.4	54	97.4±16.2	0.252
Orkney	56.3	56.1	139	96.7±16.4	177	96.4±15.1	0.857
Peebles	40.7	48.4	121	100.7±15.6	102	102.3±14.2	0.444
Perth	42.7	47.4	1010	102.4±15.2	844	101.7±14.6	0.318
Renfrew	38.8	38.4	3053	99.9±14.7	1956	99.8±14.7	0.804
Ross & Cromarty	46.6	49.8	519	96.3±16.0	480	96.0±16.0	0.816
Roxburgh	40.9	44.3	387	102.4±14.2	287	101.8±13.5	0.568
Selkirk	47.6	47.8	202	100.6±15.5	183	103.9±13.7	0.026
Stirling	46.0	45.1	1681	100.5±14.8	1414	99.9±13.8	0.251
Sutherland	47.1	49.6	113	102.2±17.1	106	101.2±13.6	0.626
West Lothian	47.4	49.9	906	98.0±14.3	858	97.8±15.2	0.789
Zetland	56.6	53.2	138	100.8±16.1	172	101.1±15.5	0.854

Data for Angus, Fife, and Wigtown were not available in the original 1932 SMS dataset.

Table S2. Comparing dementia ascertainment from mortality records with diagnoses recorded on hospital discharge

		Hospital discharge data					
		Men			Women		
		No dementia	Dementia	Total	No dementia	Dementia	Total
Mortality records	No dementia	17970	233	18203	16040	375	16415
	Dementia	366	703	1069	624	1286	1910
	Total	18336	936	19272	16664	1661	18325

Table S3. Sensitivity analysis – Scottish models – estimating underdiagnosis of dementia using primary care records

		Men			Women		
		Primary care records			Primary care records		
		No dementia	Dementia	Total	No dementia	Dementia	Total
Record linkage	No dementia	6	4	10	12	13	25
	Dementia	4	4	8	3	11	14
	Total	10	8	18	15	24	39

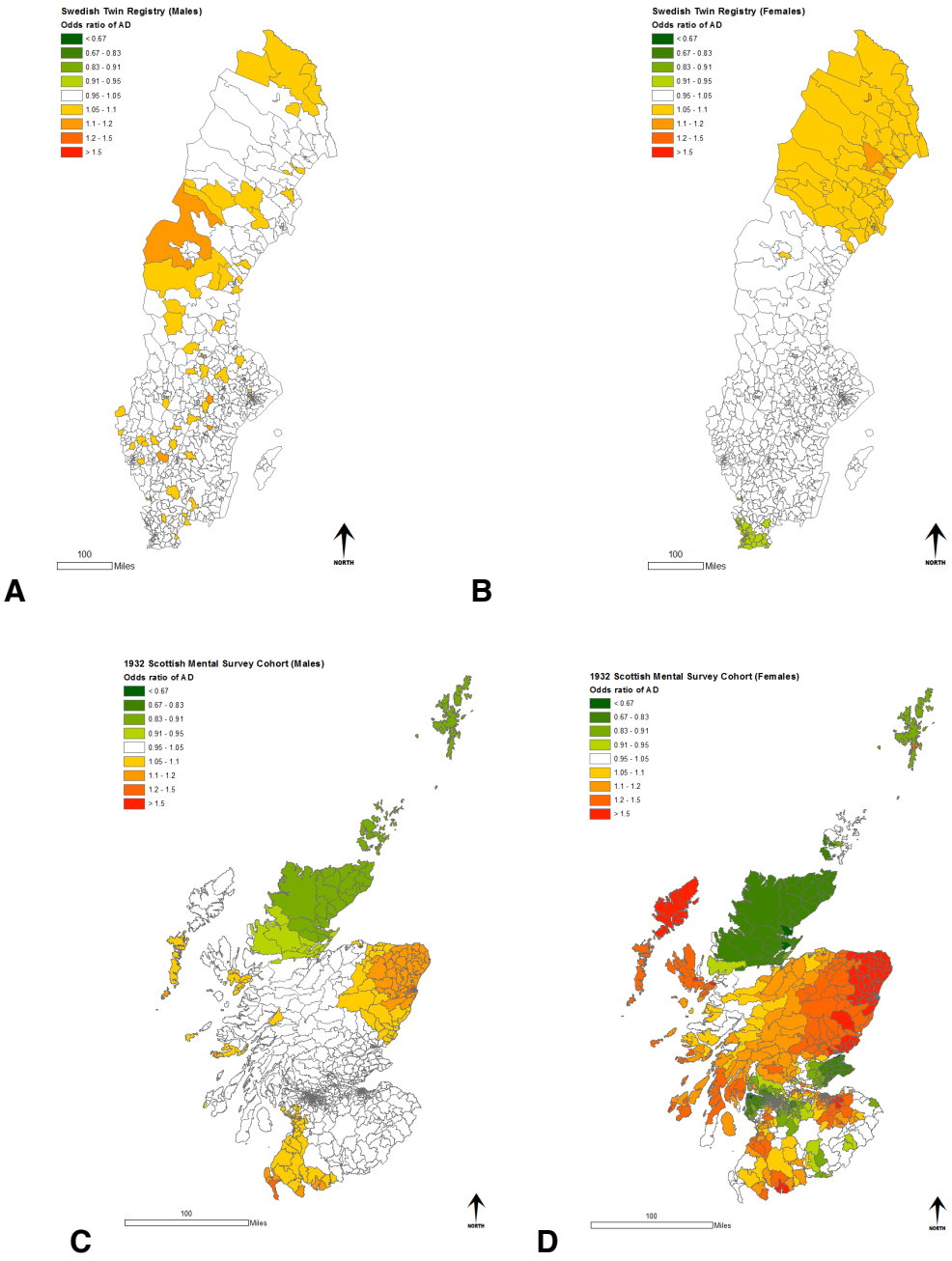

Fig. S1. Age -adjusted area effects for Alzheimer disease in the Swedish Twins (A male, B female) and in the SMS1932 cohort (mid-life location; C male, D female)

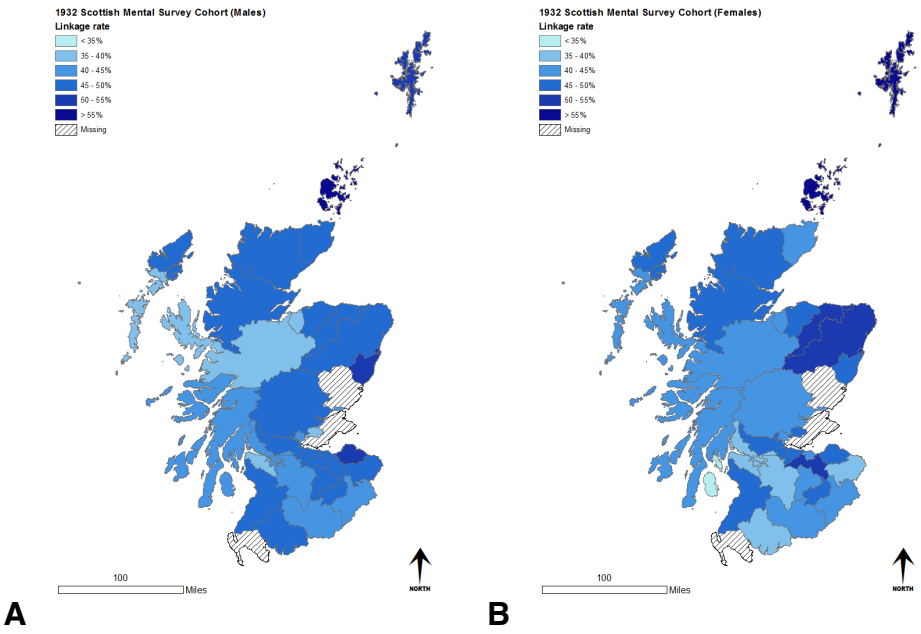

Fig. S2. Rates of record linkage in men (left) and women (right) in the 1932 Scottish Mental Survey Cohort by county of school attended age 11. Data for Angus, Fife, and Wigtown were not available in the original SMS1932 dataset

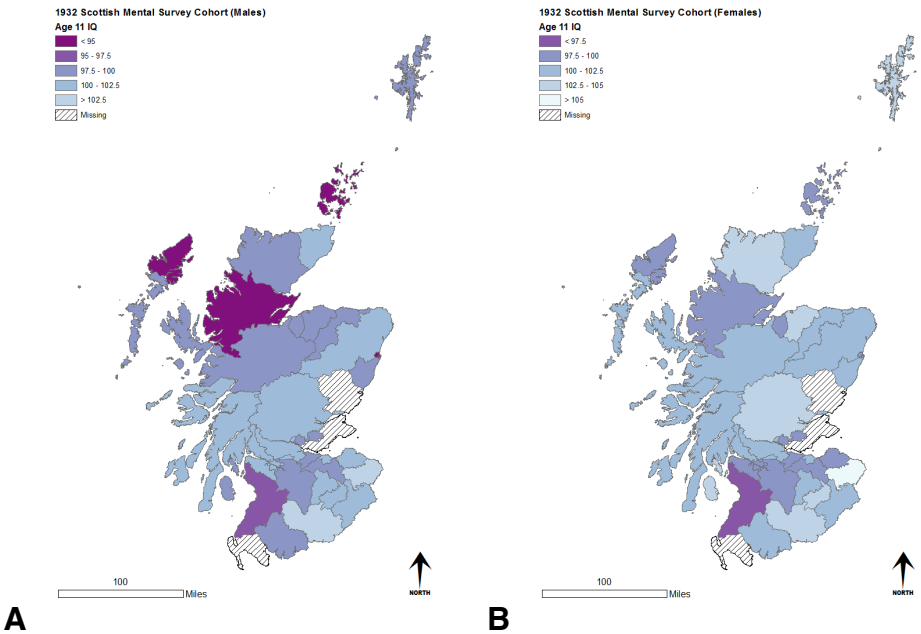

Fig. S3. Map of IQ at age 11 by county (whole cohort). Data for Angus, Fife, and Wigtown were not available in the original SMS1932 dataset

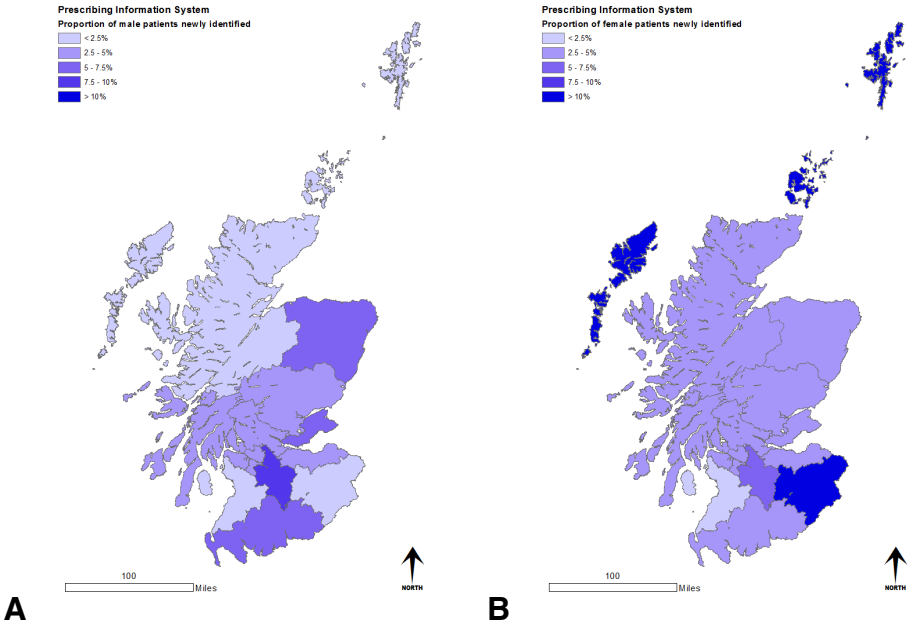

Fig. S4. Rates of patients born in 1921 with dementia newly identified by the Prescribing Information System as having been dispensed one or more prescription item for a drug for dementia (a cholinesterase inhibitor or memantine) and who were not identified by hospital admission or mortality records as having been diagnosed with dementia (A male, B female). The definition of dementia used was identical to the one used in the main study (ICD-10 codes F00-F04, F05.1, F09, G30, and G31)

Fig. S5. Posterior probability of disease mapping models in Swedish twins (A male, B female); the SMS1932 cohort in childhood (C male, D female); and the SMS1932 cohort in mid-life (E male, F female)

Appendix D

R syntax for individual participant meta-analysis

```
library(survival)                    # Package for Cox regression
library(metafor)                     # Package for meta-analysis

# Create output table with one row for each meta-analytic model
output = matrix(NA, n, 7)

# Create result table with one row for each study-specific model
# These will then be meta-analysed to give an overall result
result = matrix(NA, m, 2)

# Study-specific models with separate datasets
cox1 = summary(coxph(Surv(survival, dementia==1) ~ covariates,
                                                        data=dat1))
result[1,1] = cox1$coefficients[1,1]
result[1,2] = cox1$coefficients[1,3]
...
coxm = summary(coxph(Surv(survival, dementia==1) ~ covariates,
                                                        data=datm))
result[m,1] = coxm$coefficients[1,1]
result[m,2] = coxm$coefficients[1,3]

nevent = cox1$nevent + ... + coxm$nevent
n = cox1$n + ... + coxm$n

# Meta-analyse study-specific effects
ma = rma(as.numeric(result[,1]), sei=as.numeric(result[,2]),
                                        measure="GEN",method="REML")

# Extract coefficients of interest
output[a,1] = "Model description"
output[a,2] = nevent                 # number of disease events
output[a,3] = n                      # total N
output[a,4] = exp(ma$b)              # hazard ratio
output[a,5] = exp(ma$ci.lb)          # lower 95% confidence interval
output[a,6] = exp(ma$ci.ub)          # upper 95% confidence interval
output[a,7] = ma$pval                # P value
```